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DERMATOLOGY OF THE ANCIENTS*

HOWARD FOX, M.D.

NEW YORK

The present condition and the future prospects of dermatology have been ably discussed by former chairmen of this section. Since Hippocrates has said that the physician must know what his predecessors have known, if he does not wish to deceive both himself and others, it has seemed to me that an account of the dermatologic knowledge of our earliest predecessors might prove of interest if not of practical value.

An historical sketch of dermatology of the ancients properly begins with the Egyptians, as there is no doubt that the written account of their civilization is the oldest that is known. According to Comrie,[1] the medical practitioners in the early days of Egypt belonged to a learned class, enjoyed a high social position and were in many cases the friends and counselors of kings. This is shown by monuments that were erected to them, one of their number, indeed, I-em-hotep (3000 B. C.) having been later deified. As a rule, however, the names and personalities of the physicians, however skilful or famous they may have been, remain unknown.

The source of our knowledge of ancient Egyptian medicine is mostly derived from six papyri, all having been discovered and deciphered within recent years. The most important of these is the famous Papyrus Ebers,[2] a manuscript nearly 65 feet in length. It consists of 108 columns (or pages), each composed of about twenty lines of so-called hieratic script, beautifully written in red and black ink. This precious document, together with five other papyri, contain in less than 185 pages a most valuable amount of information about medicine and pharmacology of the ancient Egyptians. From various data it was calculated by Ebers that the Papyrus which bears his name was written about 1552 B. C., at a period before the exodus of the Jews from Egypt. It is now generally agreed that the Ebers Papyrus is not the work of any single author but a compilation of medical knowledge of many previous centuries. Like the Hearst Papyrus, as Reisner[3] says, it is "only a collection of practical remedies intended for the use of practicing physicians."

While the Egyptians doubtless had a considerable knowledge of practical medicine, they felt that its effectiveness was increased by the addition to some of their prescriptions of various magic incantations. Many of their drugs had a real therapeutic value, while others contained various disgusting ingredients whose purpose it was to drive out the wicked demons from the bodies of the unfortunate sufferers. An example of the latter class is shown by a prescription in the Berlin Papyrus, containing seven ingredients, five of which consisted of the dung of various animals.

The dermatologist should be especially interested in the medicine of the ancient Egyptians on account of the prevalence among them of skin diseases. We learn of this indirectly from Pliny and other writers, and have direct evidence from the numerous references to diseases of the skin and scalp that appear in the medical papyri. In a tabulated list of various diseases in the Papyrus Ebers, von Klein[4] mentions, among diseases of the scalp, "tumors, alopecia and eruptions," also prescriptions to prevent hair from turning gray, to produce its growth on bald heads, to promote the growth, to make it grow on cicatrices, to depilate the scalp and to dye the hair. Under facial diseases he mentions sunburn, freckles, wrinkles, discolorations, roughness and blotches; under diseases of the skin, pustules, prurigo, swellings, tumors with fetid suppurations, leprosy, eczema, scabies, itching cankers, boils and carbuncles. In addition, von Klein mentions gangrene, eschar formation, burns, spots or white cicatrices which such sores leave and alteration of the hair on the burnt surfaces, perspiration of the feet, sore toes, corns, bunions, callosities of all sorts and falling nails. In Chapter 12 of the Hearst Papyrus there are thirteen remedies, according to Reisner, "relating to the hair and skin, etc."

Some of the dermatologic prescriptions in the Ebers Papyrus are extraordinary, to say the least, in their composition. As an example, equal parts of the toes of a dog, ripe dates and asses' hoof were suggested as a remedy to make hair grow, the ingredients first being boiled carefully in a pan of oil. Another prescription for baldness, that has been frequently quoted, consisted of equal parts of cerebrospinal fluid and writing ink. Perhaps the most unusual recipe for the cure of baldness consisted of equal parts of the fat of a lion, hippopotamus, crocodile, goose, snake and ibex. Thus we see that goose grease, which has recently been recommended as a very penetrating ointment base, is not particularly new to the medical profession. Most of the ancient Egyptian prescriptions were ordered to be taken for a period of not more than four days, a fact that might account for the prevalence of skin diseases which, as we know,

* Chairman's address, read before the Section on Dermatology at the Sixty-Sixth Annual Session of the American Medical Association, San Francisco, June, 1915.

1. Comrie, J. D.: Medicine Among the Assyrians and Egyptians in 1500 B. C., Edinburgh Med. Jour., 1909, ii, 101.

2. Ebers, G. M.: Papyrus Ebers, Das Aelteste Buch über Heilkunde (German trans. by Joachim), Berlin, 1890.

3. Reisner, G. A.: The Hearst Medical Papyrus, Leipzig, 1905, p. 4.

4. Von Klein, C. H.: The Medical Features of the Papyrus Ebers, THE JOURNAL A. M. A., Dec. 23, 1905, p. 1928.

are so often distressingly chronic. While most cases of scabies might have been cured by appropriate treatment of four days, we hate to think of the disappointment of the sufferers from psoriasis or chronic eczema, whose physicians felt content with such a short course of treatment.

"The question of syphilis," writes Comrie, "has been raised in connection with the advanced atheroma that has been found in the large arteries, the diffuse signs of periostitis and particularly in regard to a case of ulceration of the skull described recently by Professor Lortet. No absolutely conclusive evidence as to the existence of this disease in early Egypt has, however, yet been found, and Professor Elliot Smith has demonstrated that the supposed ulceration is probably due to the attack of insects ages after the bones were buried."

That specialism in medicine is not confined to modern times is shown by the account of Herodotus, who was one of the two chief authorities on Egyptian medicine in the fifth century before Christ. Referring to the medical practitioners of Egypt, Herodotus says, "The art of medicine is divided among them. Each physician applies himself to one disease only and not more. All places abound in physicians. Some physicians are for the eyes, others for the teeth, others for the belly and others for the internal disorders." The fame of at least one Egyptian specialist in skin diseases, it appears, was great enough for him to be summoned to Greece in consultation.

The conception of medicine among the ancient Egyptians was certainly much broader than that of the present day. Thus the subject of cosmetics was not considered beneath the dignity of the profession to practice as a special art. According to Paschkis, identical substances that are in vogue today as cosmetics were used thousands of years ago in Egypt. No less a personage than Cleopatra is said to have written a treatise on the subject, which has unfortunately perished. Furthermore, the duties of the medical fraternity included the work that is nowadays performed by professional vermin exterminators, and we find in the papyri recipes for preventing bees from stinging, flies from biting and rats from eating corn.

Among the ancient Hebrews the art and science of medicine occupies a peculiar position from the fact that all of our knowledge on the subject is derived from nonmedical sources. There were no ancient Hebrew books devoted especially to medicine, and we cannot properly speak of a system of Hebrew medicine comparable to that of the ancient Egyptians, Hindoos or Greeks. The sources of our information are chiefly the Bible and Talmud. The oldest Hebrew literature was the Pentateuch or Mosaic Law, revealed to Moses by Jehovah on Mount Sinai, and centuries after committed to writing. According to Jewish belief, other revelations beside this "written law" were made to Moses, which were handed down from generation to generation as oral traditions and eventually compiled and recorded in the third century of the Christian era. This compilation was known as the Mishnah, and consisted of a "collection of binding precepts and legal decisions deduced by the ancient rabbis from the Pentateuch and itself forming a second or oral law." In the course of time, numerous commentaries and discussions relating to the Mishnah were also compiled and committed to writing, which were known as the Gemara. The Mishnah and Gemara together constituted the Talmud, of which there were two, the Palestinian and Babylonian Talmuds. Of these the Babylonian Talmud was much more voluminous and of somewhat later date than the Palestinian compilation, being completed about the sixth century A. D.

The references to medical subjects in the Bible and Talmud deal mostly with the prevention rather than the treatment of diseases, and the remark of Bennett[5] seems quite proper that "the Mosaic sanitary code may be said to constitute the basis of modern sanitary legislation." One of the functions of the priest, who may be considered as a sort of health officer, was to decide whether a skin disease was "clean" or "unclean," though nothing is said about his having to treat these diseases. While it is quite likely that the priests and some of the prophets had more or less medical knowledge, the practice of medicine, such as it was, was carried on by the physician or rophé. That the esteem in which the physician was held varied considerably may be seen from a saying in the Talmud that the proper place for the best physician was in Hades, while according to another more flattering saying, the wise man was advised not to live in a town that has no physician or bloodletter.

Before discussing particular diseases of the ancient Hebrews, I should like to mention the difficulty of their recognition as pointed out by Higier.[6] As this writer says, we are often puzzled at the present day to make a diagnosis when a patient is presented to us for examination with a full history. When a history alone, without the patient is presented, our difficulties increase. When, however, the history was written many centuries ago by physicians whose terminology and conception of medicine were different from our own, we are still further embarrassed. But when such ancient histories of disease were written by laymen, we must admit in most cases our complete helplessness in making a proper diagnosis. It is such difficulties as these that are encountered in the study of biblical leprosy.

To the modern dermatologist, the subject of leprosy as described in the Old Testament is as fascinating as it is difficult. The question to be settled is whether the disease described by Leviticus as Zaraath and translated as leprosy in the Authorized Version really refers to the modern disease leprosy, with which we are all familiar. The thirteenth chapter of Leviticus contains fifty-nine verses which consist of hard and fast rules for the differentiation of leprosy from harmless diseases of the skin. An idea of their medical value may be obtained by reading the following verses:

1. And the Lord spake unto Moses and Aaron saying
2. When a man shall have in the skin of his flesh a rising (sëeth) a scab, (sappachath) or bright spot (bahéreth) and it be in the skin of his flesh like the plague of leprosy; then he shall be brought unto Aaron the priest or to one of his sons the priests:
3. And the priest shall look on the plague in the skin of the flesh: and when the hair in the plague is turned white, and the plague in sight be deeper than the skin of the flesh, it is a plague of leprosy: and the priest shall look on him and pronounce him unclean:

Reading further, we are told that if the symptoms of white hair and depression of the patches are not present, the individual is to be isolated for further

5. Bennett, Sir R.: The Diseases of the Bible, 1887.
6. Higier, H.: Was lehren uns die Bibel, der Talmud, und das Evangelium über Lepra und Syphilis? St. Petersburg Med. Wchnschr., 1907, xxiv, 67.

observation, and if at the end of two weeks the "scab" has spread, the case is pronounced leprosy.

McEwen,[7] who has recently written a most interesting and careful analysis of the subject, says that the "differential criteria, white hair, depression and spreading, are absurdly insufficient to constitute a dividing line between harmless skin diseases and leprosy." He then proceeds to tabulate the eleven pathologic conditions of the skin mentioned in the remaining verses of the chapter, which he states are "far too scant effectually to distinguish leprosy from the many other skin diseases which must have been prevalent at that time." With this opinion, I most heartily agree, as also with that expressed by my father, Dr. George Henry Fox,[8] who said in referring to the Mosaic law that "there are no scriptural references to any disease which is unmistakably the leprosy of the present day." If the description in Leviticus does not accord with the conception of modern leprosy, how much less do certain miraculous statements convey the idea of this disease, as when we read in Exodus 4-6, that Moses put his hand into his bosom at the command of the Lord "and when he took it out, behold his hand was leprous as snow."

Various modern writers, including von Bärensprung,[9] Danielson, Neumann,[10] and Bloch,[11] consider the Zaraath of the Bible to have been true leprosy. Preuss,[12] who is an authority on the medicine of the Bible and Talmud, is also of this opinion, and calls attention to the chronicity of the disease, to the fear in which it was held and to the fact that its victims were not bedridden. He argues that there are only two diseases, namely, syphilis and leprosy, which could inspire such fear, and, by the easy exclusion of syphilis, concluded that the disease Zaraath referred to true leprosy. On the other hand, Münch[13] considered the disease to be an endemic vitiligo, and Katzenelson and Sack[14] thought it a form of dermatomycosis from the references to spreading of the lesions and to leprosy of garments. Finaly[15] thought it syphilis, while Ebstein[16] considered that Zaraath represented a composite name for various skin diseases that cannot now be recognized.

While it thus seems difficult or impossible to understand the significance of the word Zaraath from a medical standpoint, a more reasonable explanation is afforded from the religious point of view as expressed in the conclusion of McEwen[17] that "the word leprosy did not refer ever and always to true leprosy, but was rather a generic term covering various sorts of inflammatory skin diseases, which rendered the one afflicted unfit to associate with others, not because his condition was contagious as a disease, but because by virtue of the belief among the Hebrews in the principle today known as 'taboo,' it disqualified him for the worship of Jehovah, threatened others by contact with a like disqualification, and required ceremonial procedure for removal."

Among the references in the Bible of dermatologic interest may be mentioned the disease with which Job was afflicted. We read in the description that he was smitten by Satan "with sore boils (schechin ra) from the sole of his foot unto his crown," and, furthermore, that "he took him a potsherd to scrape himself withal." It would seem that a diagnosis of boils would hardly be compatible with the pruritus that would cause the patient to sit in the ashes, as we read, and scratch himself with a piece of pottery. From a consideration of the entire narrative, Preuss considers the disease of Job to have been a universal eczema.

An interesting case of hypertrichosis is mentioned in the Bible in the person of Esau, the twin brother of Jacob, who at his birth was "all over like a hairy garment," and of whom Jacob later said "Behold, Esau my brother is a hairy man and I am a smooth man."

The medicine of the ancient Hindoos ranks next to that of the Egyptians, Babylonians and Hebrews in point of antiquity. It is superior to the former, according to Baas,[18] and not far behind Grecian medicine in the extent and elaboration of its doctrines. The oldest and most celebrated treatises on Hindoo medicine that are now extant are the Charaka Sauhita and Susruta Ayurveda. "An older work," writes Dutt,[19] "called Ayurveda is mentioned in both these works as having formed a part of Athar Veda. It is said to have been originally composed by Brahma the Creator and to have consisted of a thousand chapters and a hundred thousand slokas. Afterward in consideration of the short lives and small intellects of human beings it was abridged into eight chapters. The Ayurveda with a hundred thousand slokas is probably a myth, but the Ayurveda with its eight divisions seems to have had a real existence although it is not available at the present day. It probably became obsolete after the works of Charaka and Susruta were composed." The works of Charaka and Susruta are supposed to be commentaries on the Ayurveda, and though written by men, are given divine origin. Thus, it is said that Charaka was prepared by Atreya, who was instructed by Indra the King of Heaven, while Dhanwantaree, the physician to the gods, imparted his knowledge to his pupil Susruta. Charaka is the more ancient work, and is thought by many to have been written about the time of Christ. Susruta was probably of later origin, and is especially noted for its attention to surgery.

The relation of all the ancient systems of medicine to the priestly class is nowhere better shown than in India, where the art of medicine was controlled by Brahmins, although for a time Buddhist priests contested their supremacy in this field. Medicine in ancient India was very highly respected, as may be judged by the saying that one of the fourteen precious objects which their gods are believed to have produced by churning the ocean was a learned physician. While the Brahmins themselves were philosophers and teachers, the actual practitioners of medicine were the Vaidyas or a sub-caste of the powerful and aristocratic Brahmins.

7. McEwen, E. L.: The Leprosy of the Bible in Its Medical Aspect, Biblical World, 1911, xxxviii, No. 3.
8. Fox, G. H.: Biblical and Modern Leprosy, Pop. Sc. Month., 1884, xxiv, 797.
9. Von Barensprung, F.: Die Hautkrankheiten, Erlangen, 1859, p. 1.
10. Neumann, I.: Lehrbuch der Hautkrankheiten, Vienna, 1880, p. 1.
11. Bloch, I.: Der Ursprung der Syphilis, Part 2, Jena, 1911, p. 486.
12. Preuss, J.: Biblisch-talmudische Medizin, Berlin, 1911, p. 369.
13. Münch, G. N.: Die Zaraath (Lepra) der Hebraischen Bibel, Dermatologische Studien, 1893, xvi, 72.
14. Sack, A.: Was ist die Zaraath (Lepra) der Hebraischen Bibel? Virchows Arch. f. path. Anat., 1896, clxiv, 201.
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16. Ebstein, W.: Die Medizin im Alten Testament, Stuttgart, 1901, 89.
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18. Baas, J. H.: Outlines of the History of Medicine and the Medical Profession, New York, 1889, p. 49.
19. Dutt, U. C.: The Materia Medica of the Hindus compiled from Sanskrit Medical Work, Calcutta, 1877, p. 6.

The teaching of the ancient Hindoos in anatomy and physiology shows that they were not accustomed to dissect the human body or those of animals. In their description of anatomy it is stated that the body contains 500 muscles, though only 490 in women, from 300 to 360 bones, twenty-four nerves and, of special interest to us, that the skin consisted of seven layers or membranes. According to Wise,[20] the skin was supposed to be healthy when it was soft and had much hair.

"Hindu physiology," writes Garrison,[21] "presupposes that the vital processes are actuated by means of the air (below the navel), the bile (between the navel and heart) and the phlegm (above the heart) from which are derived the seven proximal principles chyle, blood, flesh, fat, bone, marrow and semen."

The ancient Hindoo conception of the cause of disease included many natural phenomena, such as exposure, climate, irregularity in food, exercise, etc., which were supposed to corrupt or derange the humors. They also thought that diseases could be caused by sins committed in the present or in a former life. Thus, one who killed a cow might suffer from lepra. A drunkard might be punished by a skin disease, and an incendiary by erysipelas, etc.

While we have seen that Egypt was the land of specialism in medicine often carried to an absurd extreme, the opposite condition prevailed among the ancient Hindoos. As Baas says, "Indian medical practice is distinguished from that of all other people of antiquity by the fact that it recognizes no proper specialties but simply physicians practicing general medicine." Though there were no skin specialists in ancient India, there evidently would have been plenty of occupation for such, had they existed. Many diseases of the skin are mentioned by the ancient Sanskrit writers, and this in spite of the strict regulations that were given concerning personal hygiene and diet. Such regulations involved a daily bath and inunctions with oil, especially about the head, ears and the soles of the feet. Their clothing had to be absolutely clean, as it was said that soiled clothes produced skin diseases. The nails, beard and hair were to be kept clean and cut every fifth day, etc.

Of the many diseases described by the ancient Sanskrit writers, none is of greater interest to the dermatologist than leprosy, especially as the disease is now so prevalent and severe in Asia. The early descriptions of leprosy, as in every country, appear to have included other harmless diseases of the skin. According to Wise, the "Hindoos distinguished three kinds of leprosy, a black, white and red variety and eighteen forms; seven of those are severe in their nature and eleven are mild." One of these spurious varieties is evidently ichthyosis, in which the patient does not perspire and presents large, oblong patches like the scales of a fish, rough like the skin of an elephant and of a dark brown color. Portions of the description, however, point unquestionably to leprosy, such as the hands and feet becoming stiff, insensible, ulcerating and dropping off, the nose falling in, the eyes becoming red, and the voice unnatural and hoarse

In the differential diagnosis of leprosy, the modern physician would certainly excel his ancient Hindoo colleague, though in regard to treatment he would have little to suggest, except as to the benefits of segregation. What better advice could we give than that of the ancient physician who instructed his leprous patient to "bathe, to avoid wine and fatigue and to attend to diet, take a proper degree of exercise and wear clean clothes." Some of their medicines would not be considered so favorably, as, for instance, tumeric powder in cow's urine to be taken every day for one month. The seriousness of leprosy was recognized by the ancient Hindoo physician, who classified it among the seven diseases which had a bad prognosis.

The ancient Hindoo account of elephantiasis is short but unmistakable. To quote from Wise, "It is stated that damp and cold situations produce this disease, that it attacks different parts of the body, and that it is incurable after it has remained upwards of a year, or is very large." We read of "small eruptions appearing upon the face at the time of puberty, produced by phlegm, wind and blood," evidently a description of acne. For dandruff, which is supposed to be due to deranged phlegm and wind, Susruta recommends bleeding, a rather heroic method of treatment. A remedy recommended by Chakradatta for a peculiar itching of the scrotum (possibly eczema) would not be suitable to an acute condition at least. This consists of sulphate of iron, concrete juice of the bile of the cow, sulphate of copper, sulphuret of arsenic and of antimony, to be made up in a paste with acid rice water. For the cure of external worms (pediculosis), fluid mercury is to be rubbed with sulphur until a homogeneous black mass is produced and rubbed over the affected part. Among other cutaneous affections described by the ancient Hindoo writers may be mentioned acne, boils, carbuncles, abscesses, alopecia, canities, erysipelas, urticaria, purpura, nevus, verruca, ulcers, diseases of the nails and chicken pox.

In the very extensive materia medica of the ancient Hindoos there were a good many remedies recommended which appear to us rather grotesque. Thus, it is hard to see any value in using the moisture contained in cow dung for inflammation and discoloration of the skin. On the other hand, the Hindoos deserve credit for having used arsenic not only in leprosy but also in other diseases affecting the skin. Mercury also, according to Royle,[22] appears to have been externally employed in the time of Pliny. Their external remedies included oils, plasters, poultices, baths, hot applications for inducing perspiration, fumigation for ulcers and skin diseases, and the cautery, both actual and potential.

Whatever opinion we may hold in regard to the medical knowledge of the ancient peoples of whom we have spoken, it must be admitted that the real foundations for the scientific study of medicine were laid by that remarkable race, the ancient Greeks, under the leadership of the immortal Hippocrates. Although himself a descendant of a long line of priest-physicians, Hippocrates (460-377 B. C.) was the first to separate medicine from religious superstitions and philosophical sophistries. He said that disease arose from natural causes and not from the anger of the gods. He was a great exponent of the vis medicatrix in advising us to "follow nature," and he recognized that accurate observation was necessary for all medical progress.

20. Wise, T. A.: Review of the History of Medicine, London, 1867, p. 181.

21. Garrison, F. H.: An Introduction to the History of Medicine, Philadelphia and London, 1913, p. 50.

22. Royle, J. F.: An Essay on the Antiquity of Hindoo Medicine, London, 1837, p. 15.

Without much knowledge of anatomy and little or none of physiology, it is hardly surprising that little progress was made by Hippocrates and his followers in ascertaining the essential nature of disease. Like the four elements, earth, air, fire and water, and the four qualities, heat, cold, moisture and dryness, there were supposed to be four cardinal fluids or humors in the body, the yellow bile, blood, mucus and black bile, in the order named. By a uniform mixture and adjustment of all of these, health was maintained. The basis of life was the innate heat, the evaporation of which caused death. The presence of air that was supposed to exist in the vessels was also considered essential to life. In a disease running a normal course, the process went through the stages of "crudity," "coction" and "crisis," the first being a degeneration of the fluids, the second a preparation stage for their removal and the third their actual removal.

In regard to the Hippocratic conception of skin diseases, it is not to be doubted, as Kaposi[23] has said, that certain affections were considered to be independent or idiopathic in their origin. Others were thought to consist of deposits on the skin (apostases) which resulted from certain morbid conditions of the humors within the body. In this sense the Hippocratic writers spoke of a skin disease as an eruption, a breaking out or an efflorescence (exanthema). They looked on many diseases of the skin as curative attempts of nature which should not be disturbed, as otherwise the morbid condition might return inward or be "driven in," to use an expression that is frequently heard at the present day among the laity. While mainly considering skin diseases from the humoral-pathologic standpoint, Hippocrates also discussed the etiologic effect on them of age, sex, climate, seasons and even the weather.

As Rayer[24] says, Hippocrates "enquires into the symptoms of eruptions rather than attempts to describe them." Indeed, from his descriptions, it is difficult for us to judge of the original meaning of the terms, many of which are still in use in our dermatologic nomenclature. The form and color and certain features are often mentioned, but there are no exact descriptions of appearance and locality of skin disease.

In a critical study of the names of skin diseases used by Hippocratic writers, von Bärensprung says that the word "exanthemata" is used to refer without distinction to the "most diverse, acute, and chronic, itchy and non-itchy, dry and moist, flat and vesicular forms of eruption." Under this general conception are included three groups of disease. The first of these are the phymata, to which belong "all boils or tumors that rise upon or under the skin and gradually undergo suppuration." In this class are included furuncles (dothienes and terminthoi). The second group of diseases consists of the dry, scaly eruptions, the lopoi (from lopos the epidermis and lepo to scale). This includes lepra (which was doubtless psoriasis), lichen and pityriasis. A third group of exanthemata helchodea comprised the moist eruptions such as kerion, and achor, the moist eczema occurring in the scalp and face of children and eruptions consisting of vesicles or pustules (phlyctenai).

Attention is also called by von Bärensprung to the broad conception that was intended for the words "herpes" and "psora." Herpes referred to eruptions that gradually crawl or spread from a given point. One variety, herpes esthiomenos, appeared to be synonymous with phagedaina, a term with which we are all familiar. By psora was understood every pruritic eruption, whether dry or moist in character. Among other Greek names that are now in common use for skin diseases may be mentioned erysipelas, gangraina, petechia, ephelide, ecthyma and alopecia.

Among the famous aphorisms of Hippocrates which have been commented on by such a host of writers for the past 2,400 years may be mentioned several of dermatologic interest. Hippocrates says, for instance, "In dropsical persons, ulcers forming on the body are not easily healed," a statement with which all will agree. Again he says, "It is better not to apply any treatment in cases of occult cancer, for if treated the patients die quickly, but if not treated they hold out for a long time." Accepting the view of the ancient commentators that "occult" may mean deep seated, Adams[25] says that the conception of this aphorism will be that when cancer is superficial it can be removed by knife or cautery, but is best left alone when it is deep." In some of the aphorisms the meaning is not very clear, as in the statement that "broad exanthemata are not very itchy," or that "patients who have become bald are not subject to large varices, but should such varices supervene upon persons who are bald, their hair again grows thick."

One of the case histories of Hippocrates that is of interest to the dermatologist was that of a man who had suffered severely from general pruritus and thickening of the skin. Failing to obtain relief he went to the island of Melos where hot baths were to be found. We then read that he was cured of his pruritus and thickening of the skin but unfortunately developed dropsy and died, a statement that illustrates the honesty of Hippocrates, in consequence of which he was spoken of by jealous rivals as a practitioner of the "medicine of death."

If the reputation of the ancient Romans depended on their medical instead of their military and political achievements, we would indeed have a poor opinion of their genius. There was no such thing as a Roman system of medicine, and, indeed, there were comparatively few Roman physicians. The practice of medicine was almost entirely in the hands of the Greeks, who were responsible for all scientific progress and most of the literature. Before the appearance of Greek physicians, the Romans, as Pliny says, had gotten along without physicians for six hundred years, relying on simple remedial herbs, charms, etc. In their superstitious effort to be protected from illness, they worshipped innumerable goddesses of disease, among them being a goddess of scabies.

The physicians of the early Romans were looked on with contempt, and were not even entitled to citizenship until the time of Julius Caesar. The prejudice against them, however, gradually lessened until they were finally accorded unusual privileges. "The honorarium of a physician," writes Baas, "for an ordinary visit amounted to about 29 cents," though Pliny mentions a high priced physician who was paid the equivalent of ten thousand dollars by Manlius Cornutus for relieving him of a skin disease. The medical profession in ancient Rome, it may be added, was

23. Kaposi, M.: Diseases of the Skin, New York, 1883, p. 3.
24. Rayer, P.: Treatise on the Diseases of the Skin, London, 1835, xxxv.
25. Adams, F.: The Genuine Works of Hippocrates, New York, 1886, ii, 256.

not in any way responsible for the splendid achievements in hygiene, such as the building of great aqueducts, sewers and public baths, which were undertaken without their aid or advice.

While the practice of medicine, as has been said, was chiefly carried on by the Greeks, the best account of the art at that time was written by a Roman, Aulus Cornelius Celsus[26] (25 B. C.-50 A. D.). In spite of his masterly descriptions of diseases, it is even doubtful whether Celsus was a physician. He certainly did not engage in practice for a livelihood. In addition to his work on medicine entitled "de re medica" and consisting of eight books, he was the author of treatises on agriculture, philosophy, jurisprudence and history. Though Celsus made no impression on his contemporaries or the medieval writers, his work on medicine was eventually appreciated and is the only part of his writings that has survived.

The work of Celsus is of special interest to the dermatologists on account of the comparative importance given to diseases of the skin. In the fifth book, twenty-eighth chapter, of his "de re medica," a number of diseases are described with considerable accuracy and can be easily identified. They include carbuncle, furuncle, carcinoma, phagedenic ulcer (therioma, corresponding to the herpes esthiomenos of the Greeks), scrofuloderma (phygethlon) abscess, fistula, kerion, warts (achrocordon and myrmecia) and corns. A few other diseases whose identity we can probably recognize were venereal warts (thymia), acne, pustules (phlyzakia), erythema multiforme (epinyktis) and anthrax (from a remark that certain cases of carbuncle are painless.)

The terms "impetigenes" and "papulae" included eczema, while "pustulae" referred not only to what we term pustules but also lesions of urticaria and miliaria. Scabies referred to various forms of eczema, and vitiligo included three affections, alphos, leuce and melas. Of these, alphos might have been guttate psoriasis from the description, which reads, "It is called alphos when it is white; it is commonly a little rough and not continued, but appears like drops dispersed here and there. Sometimes it spreads wider leaving some places between free."

In his sixth book, Celsus describes various conditions of the hair and beard. He recommends frequent shaving for hair that falls after an illness, and adds with great truth that "no remedy whatever can prevent the heads of some people from becoming bald with age." The term "porrigo" was used for ordinary dandruff and probably eczema as well. The latter disease was also apparently included under the name "sycosis." Under the title of "area" is described alopecia areata, often spoken of as area Celsi. He writes that it is "almost folly" to cure freckles, "but it is impossible to prevent women from being nice in what regards their beauty." Other dermatologic affections that are described by Celsus include elephantiasis Graecorum, ulcers and burns, condyloma, varicose veins and gangrene.

Pliny the historian (23-79 A. D.) mentions several diseases that were not included by Celsus, among them being herpes zoster, which was described by Scribonius Largus under the title of Zona. Pliny also speaks of several unusual diseases, among them the cutaneous affection called mentagra, which some have erroneously considered to be syphilis. Caelius Aurelianus wrote about phtheiriasis and elephantiasis; while, according to Bloch,[27] who is our best dermatologic historian, the first accurate description of leprosy was written by Arataeus the Cappedocian (30-90 A. D.).

As the period of ancient history is considered to end with the fall of the Roman Empire in 476 A. D., it would hardly be proper to lengthen this address to include an account of the Byzantine and Arabian writers, who cannot strictly be classed among the ancients. It is sufficient to say that valuable contributions to dermatology were made by the Arabian physicians, especially in their account of leprosy and of elephantiasis. Rhazes (860-932) was the first to accurately describe smallpox and measles. Avicenna and Haly Abbas wrote careful descriptions of diseases of the scalp, and Avenzoar is said to have discovered the parasitic cause of scabies.

In conclusion, I hope that I have shown that the study of the history of ancient medicine is not altogether a thankless or uninteresting task. I can merely add that I not only appreciate the honor of my position as chairman but also the opportunity it has afforded me for dermatologic studies of fascinating interest.

26. Celsus, A. C.: Medicine in Eight Books, Trans. by Grive, London, 1838.

27. Bloch, I.: Aufgaben und Ziele einer Geschichte der Hautkrankheiten im Altertum, Monatsh. f. prakt. Dermat., 1898, xxvii, 605.

TRANSVALUATIONS *

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A kindly French philosopher has said that it is better to be 50 than 40 years of age, for 40 is the old age of youth, while 50 is the youth of old age. Having reached this venerable juvenility in life's journey and having passed more than half of these years in the active practice of the special branch of medicine to which this section devotes itself, your chairman feels himself in a position to scrutinize, in the light of experience, certain otolaryngologic tendencies.

If we charted human endeavor as we do our fevers, we would find that the curve displayed by progress resembles in a way that characteristic of sepsis which ends in recovery—first a high elevation, followed by a recession to below normal and then a return to the norm. Medical progress, being only a part of the whole, has displayed no exception to this rule. The introduction of a valuable innovation has been followed by an enthusiastic exaggeration of its value. Then, depressed by disappointment, its value is underrated. In the end, however, sober judgment prevails and its true value is established. The phase of overestimation, underestimation and "return to soberness" following the introduction of tuberculin and salvarsan to the medical profession may be cited as examples of the flow and ebb of medical opinion. These phases vary as to the time required in transition. In the case of tuberculin, the first period, the period of exaggerated hope, was quite short in duration, followed by a rather long period of underestimation; while in the case of salvarsan, the first and second periods were much shorter. But our observation leads us to the conclusion that not only the newer innovations are subject to these remissions of enthusiasm, but also even the oldest and most time honored are subject to

* Chairman's address, read before the Section on Laryngology, Otology and Rhinology, at the Sixty-Sixth Annual Session of the American Medical Association, San Francisco, June, 1915.

the same law. Take, for example, tympanic inflation, a procedure the value of which is still apparently greatly overestimated in the minds of many of my confrères. Not wishing to be misunderstood as being ignorant of this very valuable aid in the treatment of properly selected cases, I will state my position in relation to its value.

The middle ear may be regarded as a modified pulmonary alveolus, modified to the extent that it contains the sound-conducting mechanism of the organ of hearing, but retaining its ancient power of absorbing oxygen and giving off carbonic acid gas. Any obstruction to the admission of air through the eustachian tube will, therefore, cause a diminished gas pressure in the tympanic cavity. The atmospheric pressure in the external auditory canal will press the tympanic membrane inward to just the degree that the pressure in cavum is diminished by absorption, thus more or less dislocating the ossicular chain and diminishing its conductivity for sound waves. The conducting apparatus under normal conditions is held in such marvelous equilibrium that it transmits sound waves that transcend the power of the finest microscopic measurements. According to the amount of displacement of these various factors in this transmitting apparatus, various degrees of hardness of hearing result. If, by inflation, we can restore the ossicular chain to its normal position, immediate and marked improvement in hearing occurs, and we may infallibly judge the degree of mobility by the resulting improvement in hearing. There comes a stage, however, when inflation is absolutely ineffectual because of adhesions, ankylosis, dislocations, etc., and yet, I have known innumerable instances in which men have continued to perform this medical ceremony for months at a time, without any benefit to the patient—thus bringing discredit on themselves eventually and inviting the transmission of that discredit to otology as a whole. Let us admit at once that inflation has a very limited field of usefulness. In acute cases to prevent adhesions after the acute inflammatory process has subsided; in subacute cases to restore equilibrium while we remove the cause of tubal obstruction; to remove secretions from the tube and middle ear when perforation of the tympanic membrane has occurred—these are the principal indications for inflation. But if we are amazed at the men who endeavor to mobilize in cases of middle ear deafness when the malleus and incus are permanently fixed, what are we to think of the colossal faith of those who continue to indulge their fetish in cases of otospongiosis when the stapes is fixed in the fenestra by bony ankylosis, or when the hardness of hearing is due to dissemination of the spongifying process elsewhere in the labyrinth, or in cases of nerve degeneration. Is it faith that permits them to go so far astray, or is it ignorance of diagnostic methods?

Another correlated subject, and one of great importance, is the etiologic relationship of the nose to diseases of the ear. Far be it from me to underrate the frequency with which acute inflammations of the ear find their origin in diseases of the nose, but more frequently in the pharynx, or the influence certain chronic conditions have in perpetuating inflammatory tubal insufficiency. Nevertheless, I am convinced that the importance of the nose in relation to diseases of the ear is grossly exaggerated in the minds of many specialists. I agree with Felix Semon that:

> Even in cases of complete obstruction of both nostrils by multiple polypi, ear complications of any kind have been extremely rare in my practice. And if further evidence were needed, it is afforded by the fact that even in cases of complete bilateral congenital occlusion of the choanae by bony or membranous diaphragms, perfect hearing power and absence of any aural symptoms have been observed by others as well as by myself. You will understand, then, that I profess myself to be rather skeptical concerning the asserted great influence of nasal stenosis without concomitant chronic catarrh upon all possible ear trouble.

I do not hesitate to say that the slight variations from the normal in the septum and turbinated bodies which are so frequently seen and nearly as frequently operated on have no bearing whatsoever on ear diseases. After permanent changes have taken place in the ear, such as adhesion and ankyloses, it is futile to correct even marked abnormalities in the nose in the hope of exerting beneficial influence on the aural condition. Notwithstanding this, it is to my knowledge a not infrequent occurrence for patients to be promised restoration of hearing after the performance of such operation—again discrediting the practitioner and bringing discredit on otology.

Indeed, the accusation that there has existed among practitioners in our specialty a certain lust for operating is not without foundation. The patients come to us to have something done while we, on our part, are always on the lookout to find disease. As Dr. Goodheart remarks:

> There are times when the sick are not reasonable beings and unless they have a bottle of medicine to anchor their faith to they are in a state of unrest that is positively harmful to their progress.

And, as Semon says in commenting on this:

> This is certainly true. And, further, when with a little experience to guide one, one sees that the patient, disappointed at not getting what he wants, thinks: "That doctor does not understand my complaint," and that he is sure to fall into the hands of the topical enthusiast, or of somebody worse, who will be equally sure to mulct him in a perfectly unnecessary operation. One is confronted by the difficult question whether in the patient's own interest it would not have been better to comply with his wish and to give him something local which, if absolutely useless, would have been at any rate harmless, and would have set his mind at rest. I dare not say that this "pia fraus" must never be practiced. But against it are three very grave reasons, which I would particularly recommend to your consideration. In the first place, when prescribing some local application, which, of course, has to be repeated at stated intervals, you involuntarily become the patient's accomplice by concentrating his mind on his local sensations, whilst in his own interest you ought by all possible means to divert it from them. Secondly, you lend yourself to supporting the general notion, which you know is neither correct nor desirable, namely, that all affections of the upper air passages ought to be treated locally. And thirdly, and most serious of all, by yielding to the temptation you may unconsciously, and with the best intentions in the world, yet very actually, transgress the line between legitimate practice and quackery. Under all circumstances, therefore, the pious deception of which I have just spoken ought to be practiced only in the rarest of cases, and the doctor ought to stiffen his back and harden his heart against meekly complying with every unreasonable wish expressed by an unreasonable patient. Better, I think, to lose such a one if he will not listen to well-meant advice than to confess to yourself that you have descended to the level of habitually acting against your own better conviction.

When I began the study of this specialty it was little more than a matter of sprays and spurs, of

snares and syringes. Now, we are firmly emplaced on a broad surgical basis. No longer do we confine ourselves to intralaryngeal, intranasal or intra-aural operations, but by most radical external surgical procedures we aim to cure the most extensive disease of the nose and accessory sinuses, the larynx and pharynx, the ear and neighboring parts within the cranial cavity. This change has taken place gradually. It took years of endeavor to set the bounds of laryngoscopy, rhinoscopy and otoscopy. But latterly, by the work of Killian, Jensen and many of our own Fellows, the advance has been more rapid, so that at the present time the well-rounded and successful specialist not only must possess that special skill and dexterity which enable him to successfully examine the larynx, the nose, with the orifices of the several accessory sinuses, the ear, both by otoscopy and by means of the complex functional tests, but also he must combine with this a broad surgical knowledge equal to that of the general surgeon, and an ever-accessible knowledge of regional anatomy superior thereto.

Thus have we clearly proved our right to exist as specialists and members of the surgical department of the great science and art of medicine.

But may I express a fear that the pendulum may swing too far in the direction toward radicalism? With the technic of the external operation firmly in our grasp, are we not liable to resort to them prematurely—to forget the much that may be done by more conservative local measures? Let us not cease to cultivate to its highest development that special manipulative dexterity in the local examination and treatment of the nose, throat and ear which has made men like MacKenzie, Stoerk, Chiari, Politzer and many others, among our own members, famous, and which is followed in suitable cases by the most brilliant results.

For instance, when I hear a colleague say that he puts every laryngeal case on the table and examines the larynx by means of Killian's suspension apparatus, I am convinced that his zeal has outrun his discretion. I would make a plea to you that in our enthusiasm over direct laryngoscopy we do not abandon the cultivation of skill in the employment of indirect laryngoscopy. Nearly as much can be accomplished by the latter as the former and with not nearly so much discomfort to the patient.

The same may be said as regards operative procedures. Without constant practice in this regard, with indirect laryngoscopy that virtuosity which made the old masters so wonderfully skilful in the removal of growths in the larynx may be lost to the profession; and this, to my mind, is something to be avoided.

In conclusion, I wish to voice a fear that too much faith has been engendered by the enthusiastic members of our profession in the use of serum and vaccine in the treatment of nose, throat and ear affections. My personal experience has been most disappointing. I cannot recall one case of chronic aural trouble, in which the presence of bone affection was proved, that was influenced in any way by the administration of serum or vaccine. The same may be said in relation to diseases of the accessory sinuses. We must be careful to avoid that isolated position which was prophesied for our specialty some years ago. There are signs that this prophesy is reaching somewhat of a fulfilment. The remedy for this is a close affiliation with medicine as a whole. There is nothing so deplorable as the specialist who has lost sight of the rest of the organism and sees nothing but the special domain in which he is engaged. Advancement takes place, as I said in the beginning, in phases. Let us try to avoid overenthusiasm and zeal; let us endeavor to cultivate an unceasing sobriety with a large field of vision in our administrations to the sufferers who come to us for relief.

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INTESTINAL OBSTRUCTION

A PROTEOSE INTOXICATION *

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The poison under discussion may be obtained from the fluid above an intestinal obstruction, from a closed washed loop of small intestine or from the mucosa of a closed loop or a loop draining externally through an enterostomy wound. The intoxication which develops with intestinal obstruction or after producing a closed or drained intestinal loop is very similar, differing only in intensity. In like manner one can inject this poison into a dog and produce more or less profound intoxication, depending on the amount of poison introduced. This intoxication resembles closely that observed following intestinal obstruction. The evidence is overwhelming that an active poison is concerned in the production of the clinical picture of intestinal obstruction and of the closed intestinal loops.

The poison is found in rather concentrated form within the lumina of the closed loops of the small intestine. Dogs can be immunized by sublethal doses and can then withstand lethal doses of this poison, but the immunity cannot be carried very high. Moreover, these immune dogs can survive intestinal obstruction or closed loops much longer than controls. This immunity is associated with a developing capacity of the organ cells of the body to destroy this toxic substance. Filtered immune organ extracts, presumably containing active enzymes, can destroy this poison in vitro, but the blood of immune animals contains no such enzymes and is inactive toward the poison.

If a loop of small intestine is washed out thoroughly, its ends closed and the continuity of the intestine established around it by means of a gastro-enterostomy or entero-enterostomy, any intoxication which may ensue must be due to one of two things: (1) bacterial activity; (2) perverted activity of the loop mucosa (or both factors in conjunction).

We have been able to show conclusively that the intestinal mucosa is essential to the production of this poison because with destruction of the mucosa by means of sodium fluorid the formation of the poison ceases. Whether bacterial activity is essential to the production of this poison is less certain, but no conclusive evidence that bacteria are essential has been

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brought forward. It is certain that bacteria alone cannot form this poison.

Absorption of this poison from the intestine raises a very interesting and perplexing point. When it is noted that the poisonous substance is most abundant and easily demonstrated in the lumina of closed loops, one's first thought is that absorption must be mainly from the lumen, but this is not so. Some absorption may take place from the contents of the loop, particularly if the mucosa is damaged or inflamed, but fatal intoxication will usually result from a loop draining externally and washed daily. Moreover, the introduction of large amounts of poison into a loop will not alter the course of the intoxication and such animals show no more intoxication than controls with loops washed and left empty at the operation. The poison is not absorbed from the normal intestine. All evidence indicates that the absorption of the poison in intestinal obstruction or in closed loops will take place mainly from the mucosa regardless of the material in the lumen of the gut. Our attention should center on the mucous membrane which forms this poison and passes it into the blood stream. This pernicious activity may be carried on to a fatal termination by a mucosa which may be to the naked eye as well as the microscope quite normal except for capillary engorgement.

The *chemical nature* of this poison is of great interest, because once known it will be possible to concentrate attention on the action of similar poisons and finally uncover the best method of the body defense and cure. It is a very elusive substance and necessarily concealed in a mass of confusing materials. Many workers have hazarded guesses about this poison but it has never been isolated in anything like purity or identified. Almost all of the conflicting statements about this poison can be easily explained when it is realized that it is a primary proteose. We have been able to show that it is thrown out of a solution rich in albumins by boiling (adsorption) but that after autolysis or digestion it may be boiled without harm. Its proteose nature explains why the poison is held back in fine earthen filters, as stated by other observers, but not held back by paper filtration. The poison is not destroyed by digestion with pancreatin or fresh pancreas for a period of one week. It is not destroyed by autolysis with intestinal mucosa for a space of weeks but may be completely destroyed in months. Its reaction after intravenous injection in dogs closely simulates anaphylactic shock in these animals, but the poison cannot sensitize guinea-pigs for the characteristic anaphylactic phenomena.

Alcohol precipitates this poison and this is a most important step in the separation of this substance from the mass of extraneous material in the intestinal loop fluid. Five volumes of 95 per cent. alcohol will precipitate completely all of this poison, whether the fluid is freshly removed from an intestinal loop rich in albumins or has been digested to a clear broth. The alcoholic filtrate has been tested repeatedly and contains not a trace of the poison, but does contain the substance which produces the short initial fall in blood pressure (the "tissue extract" reaction). The alcoholic precipitate contains all of the poison. This precipitate may be extracted with ether for days without removing any of the poison and the ether extract gives no reaction when given intravenously in dogs. Water will remove all of the poison from the alcoholic precipitate and the poison goes into solution very rapidly. The residue may be filtered off, giving a clear opalescent solution. This of course contains some albumin, which may be removed in great measure by boiling in faintly acid reaction, and filtration. The resultant filtrate contains the poison, as shown by repeated experiments.

The poison may be still further purified by precipitation at room temperature with equal parts of a saturated solution of ammonium sulphate. This gives a delicate precipitate which may be collected by centrifugalization, dried between filter paper, again dissolved in water and boiled with a drop of acetic acid to remove the last trace of albumin. This gives a solution almost water clear but slightly opalescent. Dialysis of this pure solution against normal salt will remove the most of the ammonium sulphate but will not change the toxic action of the poison, which does not dialyze in the least. This pure solution gives biuret precipitates with phosphotungstic acid or saturation with sodium chlorid. Estimations of dry weight show that 100 mg. of this pure poison is sufficient, if given intravenously, to poison fatally a 15-pound dog.

This process of chemical isolation gives a *primary proteose* and eliminates practically all other substances except sodium chlorid and a trace of ammonium sulphate. Because of the fact that this proteose resists digestion it may be classed as a heteroproteose. The symptoms of proteose intoxication are identical with those of poisoning by loop fluid, and sublethal doses of other proteoses will immunize against this poison and prolong the life of dogs with closed intestinal loops, beyond the controls. The anatomic picture is the same in fatal proteose intoxication and in poisoning with loop fluid. We may assume with certainty that the intoxication of intestinal obstruction and closed intestinal loops is due in great measure to the absorption of a primary proteose from the intestinal mucosa.

It has been shown by Chittenden and Mendel that proteose injected into the blood may be excreted with some rapidity in the urine. We have not been able to detect this substance in the urine perhaps because of the small amount which is fatally toxic and because the flow of urine is inhibited after a large dose. The proteose may be changed in some manner before it is eliminated. Dogs with a trace of albumin in the urine usually show some proteose by Hammarsten's method and this introduces a confusing factor.

It is obvious that diuresis will help in the elimination of this toxic proteose and this explains the beneficial effect of salt infusions in intestinal obstruction. This brings up another point of some interest and of considerable importance from the standpoint of diagnosis.

The injection of this toxic proteose causes a great rise in the incoagulable nitrogen of the blood, which shows a curve rising with the intensity of the intoxication from a normal 30 mg. to 70 or 80 mg. shortly before death, and this change may take place in acute poisoning within a space of three hours.

Dogs with intestinal obstruction may show an incoagulable nitrogen as high as 200 mg. and about the same is true of the closed-loop dogs. The rise in incoagulable nitrogen of the blood seems to depend on the intensity and rapidity of the intoxication and is of considerable prognostic and diagnostic value.

Tilleston has reported two observations on human cases with very high incoagulable nitrogen of the blood in intestinal obstruction.

In conclusion it is to be emphasized that the intoxication of intestinal obstruction and closed intestinal loops is due to the absorption from the intestinal mucosa of a *primary proteose*. This proteose intoxication may be associated with a rise in the incoagulable nitrogen of the blood to four or even ten times normal. This fact may be of value in diagnosis and prognosis.

University of California.

ABSTRACT OF DISCUSSION

Dr. Victor C. Vaughan, Ann Arbor: Would a loop in one part of the intestine furnish the same poison as a loop in another part? Did 100 mg. kill the dog, and how was it administered? Intravenously?

Dr. G. H. Whipple, San Francisco: Yes.

Dr. Vaughan: Did Dr. Whipple make a biuret test? Is there any blood coagulation after death; any coagula found? Does it resemble beta-iminazolylethylamin in its poisonous action? Can you get an immunity by injecting small doses? I understand that boiling does not destroy it; therefore it cannot be a ferment, like the extract from the lungs, nor the ordinary extract from the epithelium of the duodenum.

Dr. Fred T. Murphy, St. Louis: In working on this problem for several years, first in the laboratory of the Harvard Medical School with Dr. Vincent, and later at Washington University Medical School, St. Louis, with Dr. Brooks, in preparation of the papers of which Dr. Whipple spoke, we thought that we had proved that this poison found in occluded loops was not a specific secretion of the mucous membrane and was not produced without the action of bacteria. The experiments which we considered as conclusive were as follows: After drainage for a long period we obtained a loop of intestine in which the content remained sterile. When obstructed no symptoms were caused and the content of the loop was not toxic. After infection had been introduced, symptoms were produced and the content became toxic. Gallbladders in which a circulatory disturbance had been caused by ligation of the cystic duct and vessels caused no acute symptoms, and the content remained nontoxic so long as bacteria were not introduced into the gallbladder; but when the content was infected by cultures from the intestinal tract, acute symptoms were produced identical with those in intestinal obstruction, and the content on injection showed the same toxicity as the content of an obstructed loop of intestine. Having these gallbladder experiments in mind, I wish to ask if in attempting to determine the specificity of this toxin any hollow organs other than the intestine had been used. In a rather cursory attempt to isolate a definite toxin from these obstructed loops, we were much impressed by the similarity between the toxin which we obtained and that which Faust described years ago in his study of the ptomains. We were unable to get anything as specific as Dr. Whipple has, and he is to be congratulated on his results.

Dr. G. H. Whipple, San Francisco: This pure substance gives a very beautiful biuret test. I may say, too, that this substance is thrown down by complete saturation with sodium chlorid. It has been thoroughly established that closed loops of the lower part of the intestine are very much less toxic than high closed loops. We do not know the reason. That is one of the difficult things to solve, which we may be able to get at by studying the activity of the mucosa. Loops of the large bowel in dogs give such slight intoxication that one can almost disregard it. The animal will live for months, and if the animal is sacrificed the large intestinal loop will be found to be filled with material that looks exactly like normal feces. The different parts of the intestinal tract have different activities as regards the production of this poison. We have attempted to get the most concentrated poison, and for that reason have used the duodenum with a part of the jejunum, varying in different experiments.

The reaction in the blood following the injection of this poison is very characteristic. There is a definite amount of antithrombin produced, as with the injection of Witte's peptone. The blood is not always incoagulable. It is notorious that the introduction of various amounts of peptone will give different amounts of antithrombin. Sometimes one may get absolute incoagulability of the blood, again only slight antithrombin production. Beta-iminazolylethylamin of Dale, mentioned by Dr. Vaughan, is alcohol soluble and nonprecipitable by ammonium sulphate; also the substance sepsine mentioned by Dr. Murphy and investigated by Faust. All ptomains are alcohol soluble, and I believe the initial treatment with five ounces of alcohol excludes all such substances. Immunity can be produced to a slight degree only. I have never been able to immunize an animal to more than a double lethal dose, and the immunity disappears shortly after production—I mean in a matter of weeks. Immunity, as we have shown already, resides in the activity of tissue cells; it is not in the blood. The immune organs can destroy this poison, or rather, extracts of those immune organs can destroy this poison in vitro. Boiling does not injure the substance. When it is boiled in a fluid containing albumin it is taken down by adsorption.

Dr. Murphy raised the point about occluded gallbladders infected by bacteria. We have never tried any such experiment, but it is quite conceivable that the action of bacteria on the injured mucosa of the gallbladder may produce toxic proteoses. I should think it would be extremely interesting to see whether that toxic substance produced in such gallbladders is a proteose or some other substance.

PROGNOSIS IN HEART DISEASE

FROM THE POINT OF VIEW OF ETIOLOGY *

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The tendency to a more scientific classification of diseases of the heart—using so far as possible the etiology as a basis — is decidedly to be welcomed. And it is a source of congratulation to us that certain of our own physicians, notably Dr. Cabot, have taken the lead in this work. This more rational classification will work for good in every phase of our study of cardiac conditions, but it is particularly to the matter of prognosis that I wish to call attention.

Prognosis in heart cases has been discussed from many angles, as, the valve involved—if it be a valvular lesion — the physical signs of decompensation, symptoms, changes in blood pressure, age of the patient, his habits, etc.; but there is also excellent ground for a discussion of prognosis in a general way, taking into account the causes of the disease process and how that process may be modified by treatment. For I use the word "prognosis" not in its narrower meaning of forecasting the ultimate issue, but in a broader sense that includes a knowledge or attempted knowledge of the processes at work and their susceptibility of modification by therapeutics of whatever sort. It is recognized that any of the causes that operate to produce heart disease may bring about similar lesions that give similar symptoms and physical signs, but these symptoms and signs will have different meaning depending on the underlying cause. And the value of appreciating the underlying cause no one will deny. An aortic insufficiency from rheu-

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matic endocarditis is a different thing from that of syphilis or arteriosclerosis—and a mitral regurgitation of rheumatic origin is different from that following dilatation of the left ventricle. Both prognosis and treatment are modified by these differences.

From the standpoint of etiology the great majority of patients that suffer from cardiac disease come under the following classification: Simple endocarditis and its resulting changes, chiefly valvular, syphilitic, nephritic and arteriosclerotic, which may be syphilitic or of renal association, or without either of these attendant conditions. There is a goodly number of other situations in which the heart comes in very justly for consideration but in which other pathology overshadows that organ in our minds at least. In this class I would put the hearts in septic endocarditis, hyperthyroidism, adherent pericardium, and other conditions, including pulmonary and bronchial disease. The first, septic endocarditis, is not essentially a heart disease and the patient does not die a cardiac death. The others have features that do not admit them to the right to be discussed here.

Heart disease in children and young adults has, in most cases, a relatively simple etiology in that the great majority arise from what we call rheumatic infection. And we so speak of them whether or not the joint symptoms are present, bearing in mind that clinically or experimentally there is ground for associating arthritis, tonsillitis, endocarditis and pericarditis, chorea and even additional lesions. We recognize of course a lack of finality in our teaching along bacterial lines, but we are no doubt justified in recognizing a close etiologic kinship in these lesions and, further, in holding to the reasonableness of speaking of simple or benign endocarditis.

There are, of course, less benign cases, even serious cases, not to be distinguished etiologically from the usual ones, as there are cases of endocarditis from other causes, as scarlet fever, diphtheria, gonorrhea; but even then we can say with Osler that "All other causes sink into insignificance before the endocarditis-producing poison of this motley (rheumatic) group." This group probably comprises nearly half, though it has not been so in my own experience, of patients who come to us because of cardiac symptoms or accidentally found cardiac defects. The prognosis in these cases assumes great importance and I am glad to say the picture is not nearly so dark as many have thought.

There stand out two main facts in the behavior of acute simple endocarditis. The first is that in the very great majority of first attacks the patients recover not only from the illness but with fairly capable hearts. The second fact, and one of immense importance, is that there will probably be a recurrence. The younger the patient the greater the liability of recurrences, the greater also the liability that the infection may be masked and unnoticed by reason of the absence of troublesome joint symptoms. In the first attack, then, the prognosis is good—not so good, of course, if pericarditis is present or probably if chorea is present. The danger, however, lies largely in recurrences: it lies to a less extent in the slow sclerotic process that may attack the crippled valve and gradually interfere with its function or produce similar changes in the orifice which it protects.

It is chiefly the children that have recurrences, and the deaths that I have seen in endocarditis of young people have all occurred, not from chronic development of heart difficulties, but in a recurrence in which were exhibited almost all the features of an acute attack with probably pneumonia or pleurisy added. In adults gradual decompensation without fresh infection is commoner, as there is also greater danger that patients of this age may develop a septic type on what has been a simple type and die weeks or months—in one instance under observation recently, fifteen months—after reinfection. Avoidance of reinfection, then, becomes of great importance; in fact in children it is almost the whole thing. How far this can be done can only be ascertained after extended clinical experience. Long before a bacterial cause of rheumatic fever was accepted the association of that disease with sore throat was well recognized. The stimulation given the subject in the last few years has shown almost as definite a relation of sore throat to the cases of endocarditis that have no arthritic signs. While other foci of infection, the teeth, for instance, may have a clinical relation to endocarditis, as yet the tonsils are thought to hold chief place. The rôle of adenoids we do not so well know. Anyhow, removal of tonsils and adenoids, I think, constitutes our best means of avoiding recurrence in endocarditis. Most patients will recover from the first attack with a rather good heart even if there is a persistent murmur: but whether good or somewhat crippled, with pallor and shortness of breath on exertion, they are proper subjects for surgery. For I cannot believe that there is as much danger in an anesthetic as there is in a recurrence. Not that a cripple will be whole after surgery, but he will have a better life expectancy.

Physicians have been keen enough to insist on the removal of foci to prevent arthritis, but they have not had the same boldness in the presence of evidences of valvular crippling. Also it is hardly realized that it is of more importance to prevent a recurrence of rheumatic fever in the young with a view to saving the heart than to saving the joints. A great deal will depend on the confidence the family doctor has in such measures and the boldness with which he urges them. It might be thought that this advice is superfluous, that it is being constantly acted on. I hardly think so. There is still on the part of many physicians too much dread of a murmur. Some good authorities seem timid. Dr. Poynton, who has done so much good work on rheumatism, writing in Osler's Modern Medicine, last edition, says: "With chronic tonsillar disease the desirability of complete removal should be considered." But this is too weak and does not sufficiently safeguard the child. In contrast with this, however, I quote the following from Hirschfelder:

> The patients almost always recover from the first attack (of endocarditis): Recurrence is especially common and is the danger against which precaution must be taken—the more so as the second attack often spreads to another valve or even to two more. . . . When the patient is still subject to recurrence of his rheumatism or tonsillitis . . . the probability that the cardiac lesion will remain quiescent is a small one.

The surgery must of course be thorough surgery.

The prognosis of syphilis of the heart is being worked out anew. That syphilis has a tendency to attack arteries, the coronary as well as the aorta and the aortic valves, has long been known and a proper valuation has been put on disease of at least some of these tissues. Until recently it has been accepted that

these changes occurred almost entirely in the later stages of the disease. The work of more recent years has brought forcibly home to us the fact that syphilis may and often does attack the heart in the secondary stage with rash and mucous membrane lesions, and that these lesions grow largely out of changes in the ramifications of the coronary arteries, thus reaching the heart muscle itself. True gumma is still regarded as rare, but no less real changes occur in various portions of the organ. Grossman stated that in some 40 per cent. of cases of secondary syphilis some heart disturbance was shown.

Brooks of New York, and his associates, have done much in their writings to develop interest in this field and seem to have made out a case of neglect on the part of physicians in general, in that they seem to have proved that early cardiac syphilis is common and that it is almost as commonly overlooked. At necropsy and by therapeutic test they have demonstrated the presence of specific lesions. It is not claimed that there are definite symptoms of cardiac syphilis that serve to distinguish it from trouble arising from other causes, but there are cases of cardiac symptoms and physical signs, especially arrhythmias and precordial pains arising, often early, in the course of syphilis—that cannot be accounted for readily on the more common ground for such symptoms and that have cleared up completely on specific medication. These writers and others believe that cardiac syphilis is much more common than is generally suspected and urge a more careful history taking and serologic examination in suggestive cases.

What are suggestive cases? If we see a patient at or under middle life developing heart difficulties we are accustomed to inquire carefully into rheumatic history, and other infections, such as influenza, are included, but we are not so careful to unearth a history of syphilis, especially if the difficulties do not seem associated with the aorta or aortic valves. Failing to get a history of rheumatic infection in some of its manifestations, whether or not nephritis be excluded, syphilis looms up as our best guess as a cause of infection; and with due respect for the proprieties, its existence or nonexistence should be at once established.

It is trite to say that a patient's statement as to rheumatism is never to be taken. The proper questions must be put to ascertain whether he has had what may properly be called rheumatic fever or its equivalent. This for the general practitioner or consultant who sees the case as a heart case. More satisfactory discovery of these luetic cardiopaths must come by way of special watchfulness on the part of the specialist in venereal diseases and the great bulk of general practitioners who treat this disease. It is common enough to have the syphilitic strip at certain intervals and have his skin and mucous membranes and lymph glands examined with great care but it is just as common to forget to examine the heart or to inquire into slight evidences of cardiac involvement. Etiologic diagnosis, then, not anatomic diagnosis, is the great desideratum. Etiologic treatment, also, not simply cardiac treatment, is the thing. Now it is probably fair to say that the prognosis in this form of heart disease is going to be in exact relation to the time at which the trouble is recognized. If known early and properly treated, clinical experience so far as reported seems to bear out the reasonable view that many cases can be completely cured. The later cases, as has so long been known in the aneurysmal and similar cases, cannot be relieved, though no doubt we modify what would be their natural evolution.

I do not think cardiac lesions, recognizable ones at least, will have as good prognosis as many other visceral changes of syphilis. The ease with which this incidence is overlooked, the delicate and important nature of the anatomic structures involved, with the development of irreparable damage before treatment is established, impair what one might think a favorable prognosis. But it is not too much to hope that the increased interest in this subject, coupled with the great enthusiasm in the treatment of syphilis engendered by modern discoveries, will materially lessen the arterial and other circulatory troubles of middle and later life. These lesions, however, when once established, belong in the class of essentially progressive, degenerative changes, and the prognosis partakes of the character naturally attaching to that class.

THE ARTERIOSCLEROTIC GROUP

To establish the fact that a heart is laboring under degenerative changes that grow directly out of arteriosclerosis is not always easy. There are certain infecting agents—such as syphilis or influenza—that may attack the heart in people of advanced years. At the same time we are usually satisfied with such etiology if we have age, gradual onset of symptoms, of which precordial pain is important, and evidences of vascular changes in other parts of the body. The pressure is often, but not always, high. If we can satisfy ourselves of the presence of myocardial changes due to arterial changes in its walls, how do we reason for a prognosis? In the presence of such pathology we are confronted with a clinical course varying from that of endocarditis of rheumatic origin, in that the tissue change is essentially a progressive affair. The conditions that predispose to arterial change will for the most part persist. Age, mental strain, bodily strain, imprudent eating, high pressure, continue to operate to the hurt of our vascular systems. These factors may be further supplemented by alcohol and syphilis. With the possible exception of the syphilitic attack, changes in blood vessels must be regarded as permanent and as a result nutritional deficiency is permanent.

It is quite true that some of the factors leading to arteriosclerosis can be abated, such as mental and physical strain, or overeating. But even these things are two-edged swords. Not every man profits by giving up business and leading the so-called quiet life. He often chafes under his restraints, and frets, or he may become too idle for his own good, or he may eat too much. I feel quite sure the stress of modern life, combined with hasty and liberal feeding, is a real factor in the apparent increase of heart cases. In the very great majority of instances there is established high pressure, vascular change and cardiac phenomena before we know anything of the case and then it is too late. Even if the doctor happens to pick up some shreds of information, as in life insurance examinations, the patient is not likely to heed his warnings. We are committed to our time and do not relish existence in Cathay.

We have no drug that can relieve, as in syphilis, the pathologic changes in these hearts. There is no recur-

rence of infection to head off as in endocarditis. I do not doubt that a kind of healing is possible after some acute changes that follow severe strain or a dilatation or a thrombosis, so that the immediate symptoms induced by the accident may greatly clear up, but they are rather sure to come again and the most that we can do is so to order life as to minimize the chance for this recurrence. If evidences of breakdown occur in pursuit of one's ordinary duties, to which one is accustomed and at which one must remain, the prognosis takes on a more serious aspect than if symptoms occur under unusual circumstances. A farmer of 66 years of age passed through a strenuous session of the legislature, losing sleep and enduring considerable mental strain. He all but broke down —with precordial distress and shortness of breath. Returning to the bucolic life and living in the way to which he had been accustomed, he comes now, four years later, feeling quite well and not short of breath.

Every such individual has the elements of a breakdown and only needs unusual strain to produce it. If he pursues his ordinary pursuits his prognosis is good. I rather feel that the prognosis is least good in those persons who have led more or less uneventful lives, with little mental or physical strain. If such persons develop myocardial symptoms, there is little that they can do to improve on their usual mode of life. There is this proviso, however, that in a limited group of persons, particularly if these troubles develop say before 55, a more active life in the open with less heavy diet may actually develop greater cardiac capacity.

The Schott treatment is suitable for a rather fair-sized group of cardiopaths of middle age. I think it is rather difficult to make selections, but I should be guided largely by the age, the absence of precordial pain, the nature of the previous life, and habits of eating and drinking. In the presence of anginoid pains I think such treatment had best be taken cautiously. In many cardiopaths of middle age and just above it is not unlikely that we overestimate the proportion of change effected by vascular disease. It occurs to me that quite a few may owe their distress to a flabby heart, as other muscles are flabby, coupled with a sluggish peripheral circulation. The high blood pressure necessitated to flush the capillaries puts a strain on a heart not educated to do hard work and gradual failure occurs. A change of mode of life to one of more active type may restore circulatory power and greatly improve the prognosis.

Eliminating the probability of actually improving the condition of the circulatory apparatus our prognosis in these cases comes to rest very largely on symptoms and the ease of their production. In many respects pain becomes an excellent prognostic symptom. We are accustomed to attach great importance to so-called true angina, but I am not sure that slight precordial pain, if easily produced, is not just as serious as the more severe attacks. I have seen some cases of severe angina drift along for several years and I have seen some slight precordial pain go out suddenly after only a few attacks. The ease with which shortness of breath is produced, the associated pathology, as of the lung, the presence of edema and many other features, affect the prognosis but have no bearing on this type of heart case essentially different from that in the other types.

The height of the blood pressure with or without renal change has a bearing on prognosis. However much we may regard high pressure as in a sense a physiologic condition, we are compelled to assume that the heart is doing more work than it can hope to keep up indefinitely. While work begets hypertrophy and increases capacity, yet in the presence of any coronary disease or probably without it—failures must come earlier than in a heart that is not called on to drive so strongly. If pulse pressure is high the danger of failure with dilatation is greater. A high pressure that cannot be brought to a lower stage by nondrugging measures carries with it a bad prognosis; not for the immediate future, probably, but life expectancy is impaired.

When the heart trouble is complicated by chronic interstitial nephritis the prognosis is no doubt affected by that circumstance, but to what extent it is difficult to say, there is such a wide variation in the behavior. Indeed, there is wide difference of opinion as to what constitutes interstitial nephritis. The anemia of that disease, the toxemia, whatever the nature, the accompanying arterial change, all probably have their bearing on the evolution of the cardiac features, but clinical observation would suggest that they must operate with very varying degrees of activity in different cases. Some certainly go to pieces rapidly; others, and not a few, have considerable lease of life.

The types of nephritis associated with edema often develop cardiac elements and the prognosis of a heart case of this association is bad. The edema, probably cardiac as well as general, increasing as it does the work the heart has to do and impairing its power to do it, the toxins of the nephritis, often very active, do not often admit of any great improvement and as a usual thing the end is not far off.

In the matter, then, of favorably influencing the prognosis in these types of cardiac failure the profession has in sight very little encouragement. It is rather their incidence that must be affected by preventive measures, but what those measures are to be is largely a matter for evolution.

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ABSTRACT OF DISCUSSION

DR. C. S. WILLIAMSON, Chicago: Dr. Witt stated that the prognosis of heart lesions depended first on the etiologic relations and much less on anatomic considerations. I should like to add that functional considerations are as important as the etiologic relations. In an article in THE JOURNAL this year, I hold it is impossible to find in a general way the functional capacity of the heart. We are familiar with the high blood pressure of renal diseases, but the cases in which it is probably most difficult to give a scientific prognosis are those in which we have a murmur when we are not certain whether it is so-called accidental, anemic, or due to organic change. I tried measuring the heart by a particular Roentgen method. With a normal individual at a distance of 7 feet, 1 inch, with the breath held, taking a picture in systole and diastole, then subjecting the patient to stair-climbing, to the extent of about eighteen or twenty thousand foot-pounds of work, I found the normal heart contracts definitely and cleanly. That has been asserted and denied first by the Schott and Nauheim school and later by others. I found the normal heart gives a clean-cut contraction of about 1 cm. Then in low grade stenoses insufficiencies, cases of definite heart lesion, I subjected the patients to exercise to the extent of their powers, and I found that about one-half of them showed a definite contraction, the other half showing some dilatation of perhaps a few millimeters. In severely damaged hearts, patients with edema and enlargement of the liver, we

found that after exercise about one-half of them still showed a contraction, and that I think is a new observation. The point bearing on the delightful paper of Dr. Witt is that we can add a certain modicum to our prognosis if the patient is capable of exercise, by taking the roentgenogram before and after. If the heart contracts down clean and squarely, a centimeter or a centimeter and a half, you may be sure the heart is comparatively sound. A leakage that contracts down well is better in prognosis than a heart of obscure lesion that does not so contract. There are many things to be considered in the prognosis of disease of the heart, but the only little thing I can add is the possibility of determining the reserve force of the heart in the manner I have indicated.

Dr. James S. McLester, Birmingham, Ala.: I have in the last two years acquired great respect for syphilis as a cause of myocardial disease. In the Hillman Hospital a surprisingly large number of our patients with heart disease give a positive Wassermann reaction. I have been particularly impressed with this in those patients presenting the syndrome which we commonly know as chronic parenchymatous nephritis. All of these show myocardial disease and nearly all give the serum reaction of syphilis.

Dr. John A. Witherspoon, Nashville: As to endocardial troubles from focal lesions, not only the tonsil is responsible for many of these acute cases, but alveolar abscesses are particularly liable to cause them. It is not safe to rely either on the appearance of the gum or the diagnosis of the dentist. Repeatedly I have sent patients to dentists and they would report the gums perfectly normal. Roentgen-ray pictures of such cases frequently revealed an abscess at the root of one or more of the teeth; possibly the entire root separated from the alveolar chamber. On removal of the affected teeth immediate improvement occurs. It does not matter how badly the heart is acting, the only thing to do is to remove the focal infection. I do not think we are ever justified in permitting the cause to remain. In the Nauheim treatment, it is the system used, associated with the baths. The diet and the regulation of the habits of the patient permit of the contraction of the heart. It is ridiculous for us to attempt to measure the heart by auscultation and percussion, when it can be done accurately only by the use of the Roentgen ray.

Dr. George E. Ebright, San Francisco: I should like to confine my remarks to acute endocarditis in children. It is true, as Dr. Witt suggests, many patients probably recover from the first attack. There are several reasons for that assumption. One is that in adults chronic endocarditis is frequently found without a history of a definite previous endocarditis. Undoubtedly many cases of acute endocarditis in children are overlooked. It is necessary in the treatment of such cases that the child should remain in bed for a sufficient length of time not only for the active endocardial inflammation to subside, but also for a sufficient length of time to allow for the subsidence of the myocardial irritability which persists longer than the active inflammation. Broadbent has suggested as the usual minimum three months, and from that to eight months or even longer; otherwise avoidable dilatation and consequent hypertrophy will ensure, resulting in later years in a cardiac cripple. It should certainly be assumed that where a primary focus of inflammation is found such as diseased tonsils or teeth, the eradication of the tonsils or the proper treatment of the dental infection is imperative, but it may not be possible to demonstrate such a focus, or the initial inflammation may be entirely healed and the endocarditis easily still continue.

Dr. W. H. Witt, Nashville: In the individual case the modes of testing the capacity of the heart are quite important. In reference to syphilis of the heart, as I intimated, it is a subject that has not been worked up as it should be, although it has received considerable study in certain quarters. I live in the South where we have a great many negroes with untreated syphilis, and while it has been known that aortitis and aneurysm are frequent in the negro, the incidence of cardiac syphilis in these untreated patients has not been so well worked out. We have set to work to determine the frequency of these conditions in untreated syphilis. In reference to treating children for endocarditis, we have been practically dependent on the advices particularly of the English physicians, along the line of prolonged rest, to give time for recovery of cardiac tone. It is only in a limited number of families that such directions will be carried out. We should try to get rid of the focus of disease, which is much more important. It is much safer to remove the focus of infection than to take the chances of no recurrence and of the patient's being good to himself and not overdoing the capacity of his heart. Focal infection as the cause of cardiac lesions is undoubtedly important in old people, but so many factors are present in older people that it is difficult to determine in many cases where the focus is. But when we can detect a focal lesion, it should be removed.

CONCERNING END-RESULTS OF GALLBLADDER AND DUCT DISEASES*

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The late Dr. Maurice H. Richardson[1] said: "Diseases of the biliary tract from diagnosis to established convalescence are attended by responsibilities of human fallibility of the highest order." It was he also who said that no two cases of biliary tract lesions will be exactly alike, and as compared with lesions of the appendix the possibilities are infinite. It is the evident difficulty of telling from the beginning the end-results of gallbladder and duct disease which has led us to a review of our cases. This review includes all the cases occurring in our private and hospital practice during the past twenty years in which a diagnosis of some lesion of the gallbladder and ducts was made. This period is happily coincident with the time when diseases of this part of the anatomy have first begun to be considered from a surgical standpoint. The report, therefore, includes both operative and nonoperative cases, of whatever pathology, which may have been found at operation or necropsy or which may have been diagnosed clinically as having a pathologic entity. It must be admitted from the outset that we cannot speak definitely of a diagnosis unless the case has come to operation or necropsy. In fact, we might suggest that even an operation does not always reveal the whole or underlying pathology. It is for this reason that the subject of this paper is made so indefinite, so far as the accepted and classical nomenclature of the pathology of the biliary tract is concerned. The report is to comprehend all cases having some lesion of the biliary tract, 193 cases with operation and 407 without operation. Every effort has been made by direct communication, correspondence and in other ways to keep ourselves informed of the conditions of those patients still living, and of the determining cause in those who succumbed soon after the operation, or of those in whom death occurred some time after the operation. It is to be regretted that our diagnosis in some cases could not be any more definite, and that the end-results cannot be reported more completely.

* Read before the Section on Practice of Medicine at the Sixty-Sixth Annual Session of the American Medical Association, San Francisco, June, 1915.

1. Richardson, Maurice H.: Remarks Upon the Diagnosis and Treatment of the Biliary Tract with Especial Reference to the Difficulties and Dangers, St. Paul Med. Jour., February, 1912.

We feel justified, however, notwithstanding these discrepancies, to present this compilation, for it may add to our knowledge of the comparative frequency of gallbladder and duct diseases as found clinically, may furnish an opportunity for emphasizing the necessity of more definite application of well-known and accepted curative measures, and it will enable us in a way to make a comparison between the results of the so-called medical treatment and of the surgical treatment. Many other points of interest appear in this compilation, such as sex, age, the relation of gallbladder and duct disease to pancreatic disease; the frequency of previous infections, especially of typhoid fever; the frequency of an associate glycosuria; the effect, if any, of diseases of the biliary tract on gastric function, the frequency of malignancy, etc. The number of cases observed by us are, of course, too few to justify our drawing any conclusions as to these interesting points. We must be satisfied by merely calling attention to their incidence in our experience.

Inasmuch as most of our gallbladder and duct cases were diagnosed cholelithiasis, it might be well to refer to the incidence of gallstone as found in large compilations taken from necropsy reports. Hesse[2] studied the postmortem material of a large hospital in St. Petersburg and among 17,402 necropsies done in ten years, found 378, or 2.17 per cent., of gallstone cases. From nineteen European and American pathologic reports, including 80,802 necropsies, he found 4,848, or about 6 per cent., of gallstone cases. The proportion of males to females was one to seven. The most frequent age, that is, at the time of coming to necropsy, was from 60 to 70 years, and of those 4,848 necropsies revealing gallstones, in only 16 per cent. were there any symptoms referable to gallstones. The old saying, "dead men tell no tales," can justly be applicable here, for it has been no unusual experience with us in cases when operations were instituted for other conditions and gallstones unexpectedly found, to get a good and satisfactory subsequent history of previous gallstone symptoms. If the patient had succumbed and no subsequent history could have been obtained, it would readily confirm misleading statistics which are advanced to prove that gallstone patients are in a great percentage of instances without symptoms. While we are not satisfied with the popular symptom complex of "fair, fat and forty with flatulence," we find in our experience, especially in so far as history taking is concerned, that gallbladder trouble and especially gallstone disease, can be diagnosed not infrequently without the cardinal classical textbook symptoms and signs.

Of the 614 cases of gallbladder and duct diseases tabulated, 193, or 31 per cent., of patients were operated on and 421 were not operated on. These 614 cases occurred among 3,487 cases diagnosed as having some pathology, or at least some decided functional disturbance of the digestive system, and in which no other diagnosis seemed satisfactory. And they occurred among 14,000 patients as they appeared in private hospital and consulting practice. From these figures it will be seen that about 4.3 per cent. of cases of all kinds presented gallbladder and duct diseases, and that these comprised about 17.2 per cent. of all patients having diseases of the digestive system. Two hundred and fifty-one were males and 363 were females. Of the gallstone cases, 163 patients were males and 283 were females, while of the cancer cases three were males and eight were females.

Of the 193 patients operated on 137 had gallstones and two had gallstones, besides being malignant. Fifty-four had a cholecystitis or a chronic angiocholitis. Of the 137 gallstone patients operated on, 83 were cured, 13 were relieved, 8 experienced no benefit, 11 died within a month from the operation, 8 died later, and from 14 we have not received any report recently. Of the 11 who died within a month from the operation, 6 were common duct cases and 5 were simple gallbladder cases. The fact that more than half of the fatal cases were common duct cases is significant. One of these had had gallstone symptoms for twenty years, another for fourteen years, two for six years and two for five years. The extent of the pathology found at the operation seemed in direct proportion to the duration of the disease. Of the eight patients who died later than one month, four died from causes other than gallstones. Four patients, on account of recurring attacks, were operated on more than one time.

Of the 54 patients having cholangitis, and who were operated on, 22 were cured, 10 were relieved, 13 received no benefit, 2 died within a month after operation, 2 died several years after the operation from other causes, and 5 could not be traced. This class of cases gave the most unsatisfactory results, largely, we think, because of the divergent pathology found. Some were cases of simple chronic cholecystitis, others were cases of cholangitis showing the various types, catarrhal, suppurating and gangrenous, while still others showed a pericholecystitis. The majority were associated with other pathology, more or less grave, which determined the results. Of the two cancer patients who were operated on, one was of the ampulla and the other of the fundus. These two, as well as the nine malignant gallbladder cases in which operation was not performed, died in due time.

TABLE 1.—GALLBLADDER AND DUCT CASES—OPERATIVE

	No.	Male	Female	Cured	Relieved	No Benefit	Died Within 1 Month	Died Later	No Report
Cholelithiasis, common duct	16	34	103	83	13	8	6	1	14
Gallbladder	121						5	7	
Cholang'tis	54	25	29	22	10	13	2	2	5
Cancer	2	0	2	0	0	0	0	2	0
Total	193	59	134	105	23	21	13	12	19

In explanation of our mortality, we must call attention to the fact that these patients were operated on by twenty-four different surgeons, under varying circumstances and conditions. They were not selected cases. We do not recall that any patient was refused operation by the surgeon unless it was to wait until jaundice had cleared to an extent, or to await the subsiding of an accompanying acute inflammatory condition. On the other hand, it is needless to say that many patients for whom operation was agreed on as the advisable procedure, refused operation, preferring to follow medical treatment or seek other advice. Otherwise, our list of operated cases would be much larger. In this respect the treatment of gallbladder and duct diseases differs widely from that of diseases

2. Hesse, E. R.: Frequency of Gallstones, Russk. Vratch, 1914, xiii, No. 9, p. 289.

of the appendix. In acute appendicitis the physician frequently can justly assume the attitude of a "hold-up man": "Be operated on now or you may lose your life"; and on account of the stress of circumstances and the absolute confidence exhibited by the physician, the patient almost invariably consents to the operation.

In gallbladder and duct diseases, on the other hand, when the patient is in greatest pain and is most willing to do anything to avoid a recurrence, he must be told by the physician, and by the surgeon if he is called, that the time is not opportune for operation until the attack is over and the acute inflammation and jaundice, if they are present, have subsided, when an operation will be advisable and necessary. Not infrequently after the attack there is such a feeling of well being that no amount of pressure will convince the patient that an operation must be done to prevent future complications. This is one explanation for the large proportion of unoperated cases in this report. It must be admitted, therefore, that the internist is probably in a better position to speak of the end-results in gallbladder and duct diseases than the surgeon. The surgeon sees usually only the operated cases, whereas the internist meets and must stay with or follow the large number of patients in whom the severity and complications of the disease prevent an operation.

In presenting the 421 unoperated cases in this report we do so with a keen appreciation of the difficulty of making a definitely reliable diagnosis, a fact to which we have already referred in the introduction to this paper. But we feel that a diagnosis of a lesion of the gallbladder or ducts is not much more difficult than the diagnosis of acute appendicitis, and probably not nearly so difficult as the diagnosis of chronic gastric or duodenal ulcer. Both of these diagnoses are frequently accepted without question before operation or necropsy. We will not enter into a description of the routine diagnostic methods which we employ. In some patients we recovered gallstones from the stools; in some jaundice was present, and many we saw in repeated attacks and observed for long periods. Of the cases comprising this group, 309 were diagnosed as possible gallstone, 103 as possible cholecystitis and 9 had cancer. In referring to our results, we will not consider any patient as cured, though some have passed gallstones and have not had any attacks since, and many report themselves "perfectly well." One hundred and fourteen are relieved, 47 declare they are no better, 13 died and 238 either were not treated or could not be followed. The thirteen patients who died were not under our observation at the time, but from what we could learn five died from other causes than gallbladder and duct disease.

TABLE 2.—GALLBLADDER AND DUCT CASES—NOT OPERATED

	No.	Male	Female	Relieved	No Benefit	Died	No Treatment or No Report
Cholelithiasis	309	129	180	114	47	13	238
Cholecystitis	103	60	43				
Cancer	9	3	6	0	0	9	0
Total	421	192	229	.....	....	22	

The group represented in Table 2 were called "not operated," largely to avoid the term "medical cases." They are properly, with few exceptions, all surgical cases. Since, however, it is difficult to interest a surgeon in a patient who will not or does not come to operation, the internist or the family physician must institute a care of the patient's diet and mode of life as well as a line of symptomatic medical treatment which will afford as much comfort as possible under the existing circumstances. This line of treatment, which was rarely the same in two cases, frequently led to a remarkable amelioration of symptoms. It is not our purpose at this time to present this part of the subject.

In making this compilation of cases many interesting points have appeared aside from those included under the subject of the paper.

TABLE 3.—AGE INCIDENCE IN GALLSTONES

Age at Operation	No. of Cases	Sex	Per Cent.	Duration Average, Years	Average Age at Onset	Age at Onset	Average Age at Operation
20 to 29	11	F 9, M 2	18	5	22	Under 40	
30 to 39	31	F 28, M 3	10	6	29	57%	
40 to 49	37	F 27, M 10	27	6	39	....	45
50 to 59	27	F 19, M 8	30	6	48	Over 40	
Over 60	16	F 8, M 8	50	15	49	43%	
All cases	122	F 91, M 31	25	6¾, 7½	36, 42	...., ...	F 43, M 50

1. The Average Age of Gallstone Patients at Onset and at Operation.—For the women the average age of onset was 36 years, and the average age at operation 43; while for men the average age was 42 at onset and 50 at operation. Most of the cases occurred between the ages of 40 and 50. The average time of existence of symptoms before operation is seven years.

2. The History of Acute Infections.—It is generally thought that a history of typhoid fever would suggest gallstones. Of the 122 cases of gallstone disease, only twenty-one patients gave a history of typhoid, and of the fifty-four cases of cholecystitis, twenty patients gave a history of typhoid. Other infections were not tabulated.

3. Glycosuria.—In the literature attention has frequently been called to the relation of gallbladder and duct disease, as well as gallstone disease, to pancreatic disease. The epoch-making work of Opie is well known. In our 614 cases we found only six patients, or 1 per cent., having glycosuria. One of these patients developed glycosuria about five years after a successful operation for gallstone associated with empyema of the gallbladder. She continued having sugar, though there were no gallstone symptoms, for three years, when she died from an accident. In reviewing our records of patients having diabetes mellitis, we find 150 cases among about 14,000 patients. In our experience, therefore, the incidence of glycosuria in gallbladder and duct diseases as compared with the incidence of glycosuria in all diseases, is only about one-tenth per cent. higher.

4. Gastric Secretion.—In June, 1910, one of us (Lichty[3]) read a paper before the American Gastro-Enterological Association on the relation of gallbladder disease to gastric function. It was attempted in this paper to show by experiments on dogs and also from the clinical material then at our command, that gallstones are usually associated with a hyperchlorhydria. We are gratified to report that our clinical experience still confirms the opinion held at that time. Of eighty-two gallstone cases in which operation was performed, in which gastric analyses were made, 73 per cent. had hyperchlorhydria, and of thirty-six cases of cholecystitis in which operation was performed, in which gastric analyses were made, 70 per cent. had a hyperchlorhydria.

CONCLUSIONS

1. From the fact that only five of the 121 patients having stones in the gallbladder operated on died, and as many as six out of sixteen having stones in the common duct died, it seems evident that early operation, before the case becomes a common duct one, is by far the safest procedure.

2. From the fact that only thirteen of 174 unoperated patients whom we have followed died, it seems evident that the nonoperative or so-called "medical treatment" has a mortality scarcely any higher than the operative.

3. From facts which are not shown in the tables, but which have frequently been observed by us, reduction of mortality should not be the sole consideration in treating these patients. Many of the nonoperated patients, on account of their extreme suffering during the attacks, and on account of anxiety and their limited diet between attacks, are leading a miserable and almost useless existence. Many are drug habitués.

4. Patients having disease of the gallbladder and ducts present great difficulties from the standpoint of conducting an accepted rational and scientific treatment. This is no doubt due to the protean character and periodicity of the symptoms, and to the peculiar traditions and attractive quackery which constantly appeal to them.

ABSTRACT OF DISCUSSION

DR. J. N. HALL, Denver: Dr. Lichty's figures, as he states, would indicate nearly as high a death rate in the patients treated surgically as medically, but emphasis should be laid on the fact that those cured surgically nearly all stay cured, while the alleged medical cures have the possibilities of trouble still with them. As in the case of the appendix, a medical recovery means ordinarily merely a remission. As in the case of the appendix again, the mortality is practically all from the complications of the disease rather than from the original illness. In the present series the mortality from the common duct stones was nearly ten times that of the cystic calculi. In a series of cases seen and operated under the earliest and most favorable conditions, a mortality of 1 per cent. is probably attainable, and without such favoring conditions, 2 per cent. has already been reported in very extensive series. Yet Hans Kehr, perhaps the greatest of the German operators, has reported a mortality of 10 to 15 per cent. in large groups of operations. It is remarkable that he should criticize American surgeons for operating too early and yet admit their low mortality rates. We have seen the appendix patient so convinced by his own observations among his friends that he comes and asks to be operated, and we may hope for a more favorable attitude on the part of the gallstone victim. Otherwise we shall still have many patients invalided with morphinism, myocarditis, stricture of the duct, septic complications, and especially cancer. It should be noted that in any large series the latter affection alone is found in approximately 3 per cent. of the cases, which exceeds a normal operative mortality in selected cases.

DR. MAX EINHORN, New York: I am also in favor of early operation in the gallbladder cases, but I do not think operation is necessary in all cases. The clinician cannot recommend operation at once in all early cases. But if attacks are frequently repeated or are very severe, then surgery is called for. In regard to medical treatment, I have found glycerin given internally has a beneficial effect on the secretory function of the liver. We can demonstrate that the duodenal contents and bile of individuals who take glycerin will not decompose for two or three days, whereas without glycerin they become putrid in two or three hours. So that as a therapeutic measure we may give glycerin in teaspoonful doses in the treatment of these cases.

DR. JOHN A. MCGARRY, Los Angeles: Dr. Lichty reported only a small percentage of his gallbladder cases in which typhoid fever was an etiologic factor. We formerly believed typhoid fever to be a very important factor in the causation of gallbladder disease. I would like to ask what other special factors he found in its etiology.

DR. J. A. LICHTY, Pittsburgh: I was rather surprised by my statistics. I live in a neighborhood where formerly we had many cases of typhoid annually, whereas now we have very little. I was expecting, therefore, to find that many gallbladder cases would prove to be of patients who had had typhoid fever, but such was not the case. I have no opinion to state at all as to etiology, except that possibly long-continued digestive disturbance, hyperchlorhydria or ulcer of the stomach or duodenum may cause changes which lead to disease of the gallbladder and ducts. As to treatment, this is not included under one subject. We of course could not stand idly by and let these patients go without care, so we have done all we could with dietetic and medical treatment, and it is surprising the results we could report in some cases, and also how decidedly medical treatment often fails. I was glad to hear of Dr. Einhorn's treatment with glycerin, but I hope it will not become known among the laity, for I recall the unfortunate results of such general knowledge in the case of the olive oil treatment and the many patients it led to delay proper treatment. I am fearful that the glycerin treatment will prove much like the olive oil treatment. I agree with Dr. Einhorn that you cannot at once say to the patient that an operation is necessary, but it does seem to me that in cases in which the symptoms speak definitely of some pathology, the operative treatment is the only rational treatment of these cases.

3. Lichty, J. A.: The Relation of Diseases of the Gallbladder and Biliary Ducts to the Gastric Function, Am. Jour. Med. Sc., January, 1911.

April Health Report.—During the month of April there were 34,125 employees in the Canal Zone. The total admissions to hospitals and quarters was 802, a rate of 282.02 per 1,000 as compared with 312.82 for March and 350.59 for the corresponding month of April, 1914. The total number of deaths was eight. Five died from disease or 1.76 per 1,000, as compared with 4.91 for the preceding month and 5.53 for the corresponding month of last year. The constant noneffective rate was 9.85. The total admission rate for malaria was 28.48 compared with 46.99 for the previous month and the total noneffective rate was 0.95 compared with 1.11 for the preceding month. Diseases next to malaria causing the highest admission rate were diseases of the digestive system, venereal diseases, disease of the skin and cellular tissue and of the respiratory system. The typhoid admission rate was 0.35 as against none for the previous month, and 2.01 for the corresponding month of the previous year. It will be seen that the health conditions were good in the Canal Zone, the admission and mortality rates being on the average lower even than usual.

FASCIAL TUBULIZATION IN THE REPAIR OF NERVE DEFECTS*

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It is difficult to determine the value of the different methods which have been employed to promote reconstruction of defects in nerves caused by accident, or to restore their continuity after resection because of painful scars, malignant growth, etc. The clinical reports are often meager and in many instances the patients have not been traced long enough to permit of any definite conclusions concerning the ultimate result. The results frequently admit of more than one interpretation. In many of the cases reported sensation and motion have not been carefully tested and often, in estimating final results, account has not been taken of the fact that sensation, and even motion, may be present, at least to some extent, in the area supplied by the nerve which has been divided or resected.

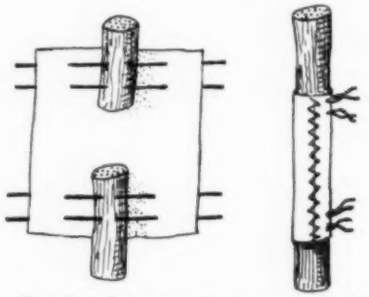

Fig. 1. — Diagram showing method of construction of fascial tube.

Vanlair[1] (1882) first suggested that defects in nerves might be repaired, if a pathway were provided, along which the axis cylinders developing from the proximal stump might pass to invade the distal part of the nerve. A number of different materials, silk protective, fresh and hardened blood vessels of the same or different species, epidermis, magnesium and hardened gelatin tubes have been used in clinical and experimental work for this purpose. That none of these is highly satisfactory is indicated by the few clinical cases in which any one has been used and by the lack of uniformity in the results obtained.

Huber,[2] after careful experimental work, came to the following conclusions concerning the bridging of nerve defects:

1. It is possible to restore functional activity to the peripheral part of a divided nerve with loss of substance, if the resected ends are united by a segment taken from some other nerve trunk, by a catgut bridge, bone drain or tubular suture.

2. The most favorable results are obtained after implantation of nerve segment, the two ends of which have been sutured with one or several catgut sutures to the resected ends of the injured nerve.

3. Regeneration of the peripheral end is the result of the outgrowth of new axis cylinders from the undegenerated axis cylinders of the proximal stump, the budding axis cylinders following the paths of least resistance to reach the peripheral part of the resected nerve.

4. That degenerated fibers of an implanted nerve segment offer much more favorable mechanical conditions to the downgrowing axis cylinders than does the loose connective tissue which supplants the catgut sutures, when this type of bridging is attempted or the bone drain, is shown by the fact that the new nerve fibers have a much straighter course and more regular arrangement in the tissue uniting the resected ends than in the case in which the latter procedures are employed.

Fig. 2.—Section of regenerated segment (within fascial tube) 1.5 cm. below level of plane of proximal section, four weeks after operation (from photomicrograph × 60).

Kilvington[3] (1908), in reviewing the literature, found that the results of homoplastic nerve transplantation were uncertain. Sherren[4] cites one success in six cases and collected twenty cases, six of which could be regarded as successful. He found record of but two cases of autoplastic nerve transplantation, one of which was successful. Kilvington experimented with free nerve transplantation and obtained poor results with heterotransplants; fair with homotransplants, and good with autotransplants. With autotransplants he obtained what he considered functionally perfect results in five out of seven cases. The gross appearance of the nerve when removed was good and there were few adhesions. In one case he bridged a gap of 2 inches in the sciatic nerve. After one hundred days there was complete recovery of sensation and motion. The value of Kilvington's work is somewhat impaired by the criteria adopted by him regarding successful results, namely, the gross appearance of the regenerated

* Read before the Section on Surgery, General and Abdominal, at the Sixty-Sixth Annual Session of the American Medical Association, San Francisco, June, 1915.

* From the Department of Experimental Surgery, Morris Institute of Medical Research of Michael Reese Hospital.

1. Vanlair: De la néurotisation du cartilage osseux dans la suture tubulaire des nerfs, Arch. de Physiol., 1882.

2. Huber, G. C.: A Study of the Operative Treatment for Loss of Nerve Substance in Peripheral Nerves, Jour. Morphol., 1895, xi, 630.

3. Kilvington: Brit. Med. Jour., 1908, p. 1414.

4. Sherren: Edinburgh Med. Jour., September, 1906.

segment, the functional recovery of the muscles and the reaction to electrical stimulation. The inadequacy of these criteria will be discussed later. Microscopic examinations were made of but four cases. Kilvington believed that the axons of the free transplant survived and assumed function. This position is untenable in the light of recent and past neurologic research, as it has been conclusively demonstrated that the axis cylinders degenerate in a free transplant and that the sheaths merely form conduits through which the newly formed axis cylinders can pass.

Fig. 3.—Distal segment four weeks after operation, showing invasion of regenerated axis cylinders, some of which are arranged in bundles (× 130).

The best results in transplantation are obtained by tissue removed from the same individual. Nerves and blood vessels frequently cannot be sacrificed to bridge defects in nerves. A tube formed of fascia, providing it did not collapse and undergo secondary cicatricial contraction would be ideal, for the supply is unlimited; a tube of any size can be fashioned to be applied to the nerve in question; and fascia when appropriate conditions are provided contracts no adhesions and remains viable.

TECHNIC OF OPERATION

After the sciatic nerve of the dog is exposed and the section removed, a piece of fascia lata of approximately the required size is removed. No muscle fiber is included. The smooth shiny surface of the fascia lying next to the muscle becomes the inner side of the tube. Some fat usually remains attached to the outer surface. In some cases the loose areolar tissue covering the fascia on the muscle side was scraped off. This seemed to favor contraction and was discontinued in the later experiments. The method of formation and fixation of the tube is indicated in Figure 1. In some experiments the nerve was exposed, cut, and the ends crushed. After two weeks or more the nerve was again exposed, the ends recovered and freshened, after which the fascial tube was applied.

Several points are deemed to be of especial importance in the technic. All trauma to nerve, fascia and surrounding tissue must be avoided. A sharp dissection should be made and hemostasis should be as perfect as possible. The suture must be applied loosely so as not to strangle any part of the nerve. Hemorrhage from the ends of the nerve must be controlled, for blood within the tube will prevent the axis cylinders passing downward. The tubes in cases in which hemorrhage occurred into them were almost occluded by scar tissue. To prevent blood passing from the surrounding tissues into the tube both end-sutures are so tied as to approximate the fascia snugly to the nerve. The tube should have a large lumen to guard against secondary contraction if this occurs. The lumen should be twice the size of the nerve end.

We have performed the operation of tubulization on the sciatic nerve of forty dogs. Ten of these are still living at periods varying from seven days to nineteen weeks after the operation. Two were discarded because of local infection and death from pneumonia. Seven specimens have not yet been studied histologically. This report is based on the study of twenty-two specimens, the animals having been killed at periods varying from one day to sixteen and one-half weeks after the operation. Most previous work on nerve regeneration has been conducted on young dogs. We have used dogs of all ages. Casts were used on the first five dogs, but not on any of the remaining.

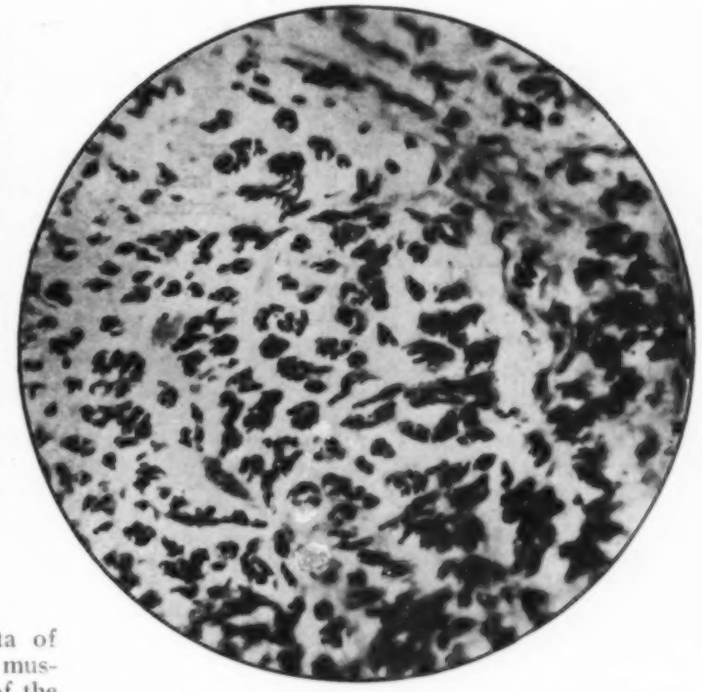

Fig. 4.—Proximal segment just above level of proximal plane of section six weeks after operation (× 325). Note enormous increase of nonmedullated axis cylinders. A few medullated fibers are seen surrounded by several nonmedullated axis cylinders (newly formed), situated under and applied to the neurilemma sheath.

The histologic technic was the following: Immediately after death the nerves were excised, stretched on

glass tubing, carefully orientated and fixed. In general two methods were employed in studying the changes, the most important being the Cajal silver method as modified by Ranson. Other pieces of the nerves were fixed with liquor formaldehydi and Zenker, and stained by Malory's phosphotungstic hematoxylin method. Hematoxylin and eosin were also employed.

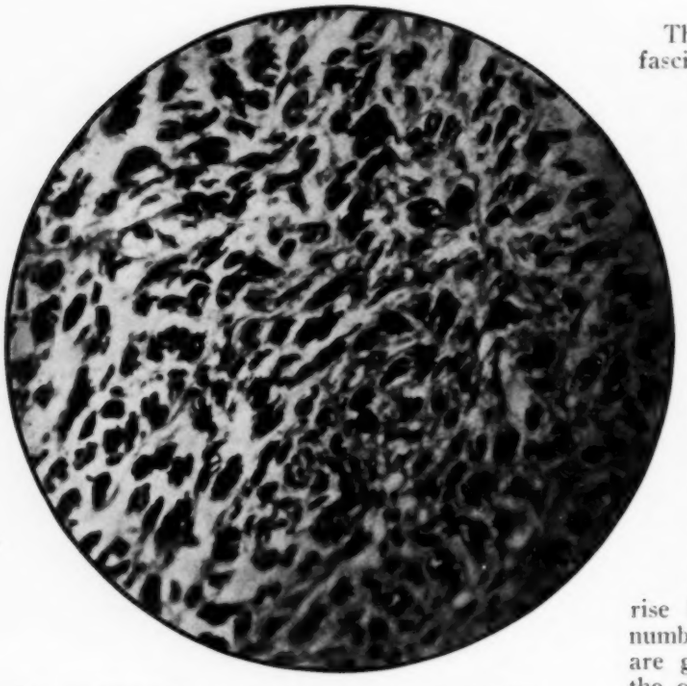

Fig. 5.—Regenerated segment six weeks after operation (× 325). Great numbers of nonmedullated axis cylinders arranged in orderly bundles are shown.

CRITERIA AS TO SUCCESS OF BRIDGING

Several criteria indicative of successful bridging have been suggested. Recovery of function, which will occur only after months when resection is made at a distance, cannot be relied on, especially when the experimental animal is a dog and the operation is performed on the sciatic nerve, for fair function returns about as soon as the postoperative tenderness is gone. The rapid return of function is probably dependent on anatomic peculiarities of innervation in the dog. Improvement in the foot drop is probably indicative of successful bridging, but as the axis cylinders have such a distance to travel, a negative result in the earlier weeks does not mean that the defect has not been successfully bridged. We have seen the foot drop disappear completely in one dog after fifteen weeks and in another dog after twenty weeks. The reaction to electric stimulation cannot always be depended on in estimating the amount of repair, for as Forsmann[5] has shown, irradiation of the current may occur, leading to contraction of muscle even when repair is not complete. The best criteria of regeneration are the gross appearance and the histologic findings.

All the specimens which we have removed have been carefully examined microscopically, after fixation, and staining methods have been employed to differentiate axis cylinders.

5. Forsmann: Zur Kenntniss des Neurotropismus, Beitr. z. path. Anat., 1900, xxvii, 407.

GROSS AND MICROSCOPIC CHANGES OBSERVED AFTER TUBULIZATION

The most interesting changes are observed in the fascial tube. At the fifth day the tube is partially filled with a soft, grayish white pulpy material resembling somewhat in appearance soft gray brain matter. No blood is found, providing hemostasis has been good, an essential to nerve regeneration through a fascial tube. Microscopically this pulpy material is finely granular and homogeneous, evidently coagulated lymph containing a few mononuclear leukocytes. The middle of the tube, that portion most remote from the divided ends, is empty. The microscopic changes in the proximal and distal stumps correspond to those described by Ranson and others in their studies dealing with nerve regeneration, and will be given but brief consideration, except in relation to the bridging of the defect.

In the eight and eleven-day stages the proliferative changes in the proximal stump of the resected nerve are marked. About one half of the medullated axis cylinders have given rise by division and lateral branching to a large number of nonmedullated axis cylinders. These are grouped in bundles of twenty or thirty about the original medullated axis cylinder. These regenerative changes involve the terminal 0.5 cm. of the proximal stump. The newly formed nonmedullated axis cylinders penetrate a little way into the pulpy material which fills the proximal end of the tube. In specimens examined after two and three weeks a solid downgrowth from the proximal stump has invaded the pulpy material. The axis cylinders develop

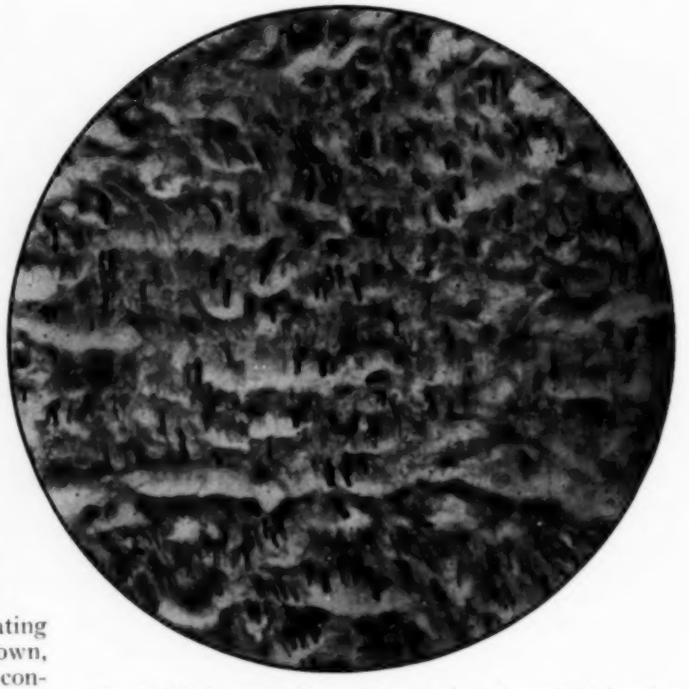

Fig. 6.—Distal segment 11 mm. below level of plane of distal section six weeks after operation (× 200). Shows regenerated axis cylinders arranged in bundles, also remnants of degenerating medullated fibers.

first and most rapidly along the side of the tube, and the nerve end, originally cut transversely, has become oblique. The axis cylinders at this stage have penetrated 1 or 2 mm. further into the ground-work of the tube than would be judged from the gross appearance. During the first week the macroscopic corresponds with the microscopic tip, but from that time on the distance to which the axis cylinders have penetrated is judged with difficulty by the gross appearance.

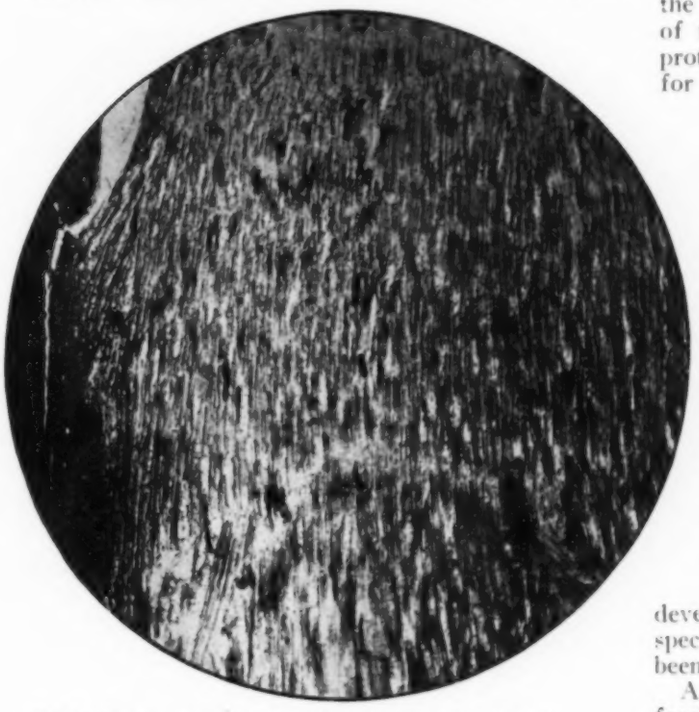

Fig. 7.—Distal segment seven weeks after operation (× 70).

After four weeks the gap, if 1 cm. or less in length, is completely filled with a firm, pearly white mass, having longitudinal striations. If the gap is longer there will still be found a part of the tube which is filled with a substance softer than the nerve, dark gray in color, into which the axis cylinders have not penetrated. At this period, in the length of gap mentioned above, a moderate number of axis cylinders have completely bridged the defect and invaded the distal segment. The axis cylinders on reaching the distal segment are no longer arranged in bundles. They are doubtless separated while passing through the material filling the tube, but the separation is mostly due to the more rapid advance of some of the fibers than of others, for in the later stages the fibers which have invaded the distal segment are again arranged in bundles.

Even at the fifth week the proliferative changes in the proximal stump and the regenerative changes are very marked. Enormous numbers of nonmedullated axis cylinders arranged in bundles of from twenty to sixty are found. Even as high as 2 cm. above the plane of section, nonmedullated axis cylinders are present in large numbers, but the medullated ones predominate. The advancing axis cylinders end in terminal bulbs at various levels. The axis cylinders which are grouped together are obviously derived from a single axon. The axis cylinders and medullary sheaths of the distal segment in the second and third weeks have undergone almost complete degeneration. Active proliferative changes in the neurilemmal cells are found, and the cytoplasm of these cells has become arranged in the form of protoplasmic bands which later will act as conduits for the advancing regenerating axis cylinders. The changes observed in this distal segment are those ordinarily noted after section of a nerve; the myelin sheath being broken up, the axis cylinders absorbed, a homogeneous matrix, evidently protoplasmic band substance being found. In the later stages, from seven to nine weeks, the distal segment contains a large number of nonmedullated axis cylinders, many being grouped to form distinct bundles, while others run singly.

That fascial tubes will remain patent and form a path for developing tissues has been demonstrated in the repair of tendons. Lewis and Davis[6] have had the opportunity of examining a fascial tube which was inserted for the purpose of permitting regeneration of the flexor sublimis and profundus digitorum tendons of the ring finger which had been lost as the result of infection. This tube, which measured three and one half inches in length, had been filled by a tendon developing from each flexor, as was shown when the specimen was examined 255 days after the tube had been inserted.

A serious objection which has been raised against fascial tubulization is contraction. If the fascial tube should undergo a great degree of cicatricial contraction, the purpose of the operation would be defeated, for the newly formed fibers would be strangulated.

Fig. 8.—Regenerated segment eight and one-half weeks after operation (× 325). End bulbs are seen at the growing tip of some of the axis cylinders. Arrangement in bundles is already well marked.

6. Lewis, Dean D., and Davis, Carl B.: Repair of Tendons by Fascial Transplantation, THE JOURNAL A. M. A., Feb. 21, 1914, p. 602.

Fascia is probably not used more frequently for neurolysis because of the fear of cicatricial contraction.

Fascia contracts immediately after being removed. This primary contraction is probably due to the elastic fibers which it contains and can be disregarded because it has reached its maximum by the time the fascial tube is inserted. The contraction which extends over a long period may be called the secondary or cicatricial contraction, and if this occurred to any extent in the fascial tubes, it would preclude the possibility of their use for nerve repair and neurolysis. There is but little secondary contraction if the fascia is sutured into place, and is subjected to the same conditions as regards stress and strain as in the part from which it was removed.

In the experimental work which has been hitherto done to demonstrate this cicatricial contraction, the fascia has been placed about the bowel, and it is probable that the changes in the fascia have been secondary to those in the peritoneum.[7] In this connection it should be mentioned that fascia undoubtedly undergoes cicatricial changes when placed adjacent to scars. Kredel has recently reported a case in which fascia was placed about an injured nerve in which there was a recent scar. Another operation had to be performed later because of pain which increased in severity, and it was found that the fascia had undergone cicatricial changes and was constricting the nerve. Kredel therefore regards it as inadvisable to use fascia for neurolysis. We believe that Kredel should not have used fascia about this recent scar. In such a case it would be better not to have attempted neurolysis, or to have resected the scar and after end-to-end suture to have performed a fascial neurolysis. Fascia in the presence of a recent scar or hemorrhage tends to undergo cicatricial contraction.

Fig. 9.—Distal segment eight and one-half weeks after operation (× 325). Utilization of old neurilemma sheaths as conduits by newly formed axis cylinders; note also grouping into bundles.

That fascia may be used successfully in neurolysis is indicated by a patient operated on by one of us (D. L.) eighteen months ago. This patient's radial nerve was cut in an automobile accident. Immediate suture was done, but an infection occurred and there was loss of radial function. In this case the scar uniting the nerve ends was resected at a second operation, and an end-to-end suture performed. A fascial flap was then placed about the line of suture. There has practically been a complete return of function following resection with suture and fascial neurolysis.

7. Kolb: Deutsch. Ztschr. f. Chir., 1913, cxxv, 399.

To avoid the possibility of cicatricial contraction, a lumen large enough for the developing nerves should be provided. The lumen of the tube in this work has been made approximately twice as large as the ends of the nerve. The fascia at first is much thicker than the perineurium, but in many cases it gradually becomes thinner and finally continuous with it. In some cases after from five to eight weeks, only the black silk orientation sutures remain to mark the original limits of the fascial tube at the ends of the gap. In other cases, as in one at four and one half months, it retains to a great extent its original characteristics; we have not yet been able to determine the factors which control this absorption or nonabsorption of the tubule.

In one case (Dog 17) the fascial tube was made so small that its lumen was less than 1 mm. in diameter, not more than one third of that of the nerve. This dog was killed six weeks and one day after the operation, and it was found that the tube had been converted into a connective tissue mass. But few regenerating axis cylinders had reached the distal stump.

In two cases veins were used instead of fascia. In one (Dog 15), a fresh segment of jugular vein obtained from the same animal was used. This procedure is more difficult than fascial tubulization. The vein wall is thinner and tears more easily when sutured. The specimen was examined after five weeks. Histologic examination showed that the endothelium and tissues of the vein wall had formed a cicatricial tissue which had grown inward and obliterated the lumen. Only a few axis cylinders had penetrated the center. Veins furnish no better results than fascia, and the technic of insertion is more difficult and time consuming.

Failures after tubulization may be due to several factors. Hemostasis must be as perfect as possible, hemorrhage from the cut ends of the nerve being carefully controlled, for a blood clot in the tube stimulates a fibroblast reaction which may be followed by dense scar formation. The soft brain-like pulp consisting of coagulated lymph and a few mononuclear leukocytes remains soft for some time and forms a bridge for the developing axis cylinders which is easily penetrated. The tube should not be applied under tension. It should be sufficiently long to be comparatively loose when fixed in position.

The reaction of fascia when placed over a recent scar has been already discussed when mention was

made of Kredel's unsuccessful case of fascial neurolysis. In order to avoid the possibility of much scar formation all dissections should be made with sharp instruments, laceration and contusions of the nerve ends and surrounding tissues being carefully avoided.

DISCUSSION OF RESULTS

Defects in nerves may be successfully bridged by fascial tubes. Histologic preparations show that the continuity of the nerve is reestablished. The medullary sheaths have not yet been formed in the specimens examined by us. These are formed late in the process of nerve regeneration.

Regeneration of the fibers which bridge the gap takes place entirely from the proximal stump, as has previously been shown by Ranson, Ranvier, Vanlair and Forsmann.

The proliferative changes in the proximal stump are very active. From fifty to one hundred times the number of axis cylinders normally found in a nerve are formed. If one out of fifty of these axis cylinders enters the empty sheaths of the distal segment it seems certain that both an anatomic and physiologic restoration of the nerve would occur. It has been demonstrated that a comparatively few axons will permit of functional activity on the part of the muscles supplied by them (Vulpius and Stoffel).

The time required for bridging depends on the length of the defect, also on the age of the animal, and the amount of tension exerted on the nerve ends. We believe that a gap of 1 cm. with proper use of this technic will be bridged in nine weeks, the axis cylinders at this time having passed well into the distal segment.

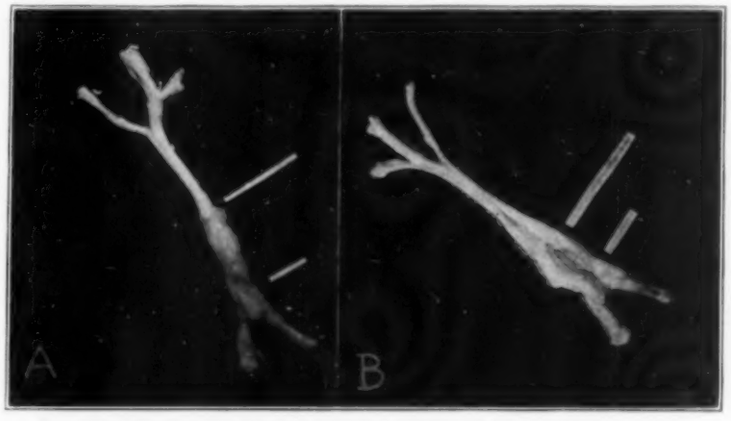

Fig. 10.—*A*, appearance of nerve removed seven weeks after operation, reduced one half. Lines indicate approximate extent of fascial sheath. *B*, same specimen divided longitudinally. Lines in fascial sheath indicate extent of former gap.

The oldest observations have been made on animals ten and sixteen and one half weeks after tubulization. Von Fleischhauer[8] in his clinical observations has found that a cicatrix in a nerve usually undergoes contraction seven or eight weeks after injury. In our oldest experiments there has been no evidence of secondary contraction in the tube. It has often thinned out so as to be almost indistinguishable from perineurium. We believe that the possibility of cicatricial contraction of the fascia is precluded when the proper technic is employed and the fascia inserted only under proper conditions.

ABSTRACT OF DISCUSSION

DR. A. A. LAW, Minneapolis: I think the simplest illustration of the tendency of the proximal nerve fragment to regenerate is shown in the neuroma. Levings showed us how, after resection of a nerve, with implantation of the severed ends between parallel muscle fibers, the proximal fragment sends out axons and causes regeneration. Forsman's theory of neurotropism explains the tendency of the nerve cells to find one another. Dr. Lewis has spoken of the various foreign bodies introduced about these nerve fragments in an attempt to aid regeneration, such as bone or magnesium, cylinders, blood vessels of men or the lower animals, Cargile and eggshell membrane, etc. These are all foreign bodies and as such must be taken care of by the host; and while they give a certain percentage of success, they are not of as much avail as autogenous transplants. The saphenous nerve resected and transplanted is interesting, but I am convinced that it is of little value over other methods, as the axons die. The blood vessels are objectionable, of which Dr. Lewis spoke, because they become occluded. In the University of Minnesota we have repeatedly wrapped sutured nerves with fascia or fat flaps. In recently operating on an avulsed brachial plexus, after section of the clubbed ends of the nerves and proper suture, we wrapped one trunk with a pedicled flap of aponeurosis and another with fat. The doctor spoke of the time element. Eight weeks ago we operated for destruction of the musculospiral nerve in a man who had been operated on four times before; after resection of the clubbed ends we found there was destruction of the nerve for three inches. Tubulization was done by fascia lata and at the end of eight weeks there was complete return of sensation and marked return of muscular control of that forearm. This fascial tube permitted nerve regeneration through it. There was a nonunited fracture of the humerus for which a bone inlay transplant was done; so we had two autogenous transplants in contact in the same field. We must conclude, then, that up to the present there is nothing available which parallels the value of fascia lata in aiding the regeneration of nerves.

DR. JOHN F. GOLDEN, Chicago: In Dr. Murphy's work we have found that the most difficult thing is to get function where we have a defect in the continuity of the nerve. We have gone through the various methods, including muscle implantation according to the method of Levin of Milwaukee, the use of catgut and the transplantation of nerve from the cadaver. The latter method we have found to be a failure. The other methods have been successful in proportion to the length of the defect in the nerve. As a later method of getting function we have been transplanting the tendons of functionating muscles into paralyzed muscles, or into the muscle which is negative through insufficient nerve supply. This has proved the most satisfactory. In neuroplastic work I should like Dr. Lewis to discuss the necessity of approximating like axons. One of the first principles in handling defects in nerves is to cut off the cicatricial neuroma that forms, or the brush-like ends, and prevent or stop any hemorrhage. The regeneration of nerves by the aid of fascial tubulation now seems to be successful, as shown by the histologic sections of Dr. Lewis, and this has perhaps solved the problem of supplying the defect in the nerve, which up to the present has had no real solution.

DR. KENITH MACKENZIE, Portland, Ore.: Four or five years ago I handled a case in which there was growing rapidly from the sheath of the sciatic nerve a sarcoma of low grade malignancy, producing disturbances which were very conspicuous. The patient complained of trouble with his foot on the affected side, which became severe. It became necessary to resect the sciatic nerve. I removed the nerve

8. Von Fleischhauer: Berl. klin. Wchnschr., 1915, lii, 212.

from the lower border of the gluteus maximus muscle and exposed the two ends of the popliteal. Following this operation there was trophic disturbance and it looked as though the leg would drop off — blebs, bullae, etc., and ulcerations occurred. In this crisis it occurred to me that I might do a neuroplastic operation, so I exposed the nerve and brought the fibers to the end of the popliteal, making first an anastomosis between the external and the internal popliteal. The flap was nineteen inches in length and it bridged the gap. The only thing I did to protect the filaments was to cover over with muscle; this is important I believe. The main effect of this operation was striking. Almost instantly the trophic disturbances ceased and color and animation came back to the leg. In four weeks I attacked the internal popliteal segment and treated it in the same way, bridged it with muscle and got primary union. There was no motion in the leg for some months afterward. One day he began to manifest signs of movement of the toes and this continued and sensation became restored, and after eighteen months the man was able to run and walk, although he had much loss of sensation. With fascial tubulization and utilization of tendons one may get recovery of function, together with sensation and motion by that operation which may seem best to do at the time.

DR. F. W. RINKENBERGER, Los Angeles: I wish to report a case bearing on this subject, showing benefit from the fascial flap. A man was caught in the gears of a motor boat and had his left arm badly mangled, both ulnar and median nerves being severed. We did a primary suture, getting success with the median but failure with the ulnar, paralysis resulting. He had trophic disturbances over the wound, in the skin, for six months. We grafted twice. At the second operation, after removing the cicatricial tissue, the nerve was too short to unite so there was a question in our minds as to the best procedure. The nerve was transplanted from behind the condyle and passed through a tunnel in the pronator group and then a fatty fascial flap thrown around the point of union, leaving the pedicle attached. The man is an ardent sportsman and I had a letter last week in which he said, "Doctor, I am able to handle my gun for the first time and I have more grip." It is too early for a final report as yet, although apparently successful the second time.

Fig. 11.—Histologic preparation of fascia at end of sixteen and one-half weeks. This fascia has undergone no cicatricial changes and is in the same condition as at the time inserted. After this length of time no contraction or replacement of the fascia is expected.

DR. DEAN LEWIS, Chicago: It is a matter of prime importance in nerve surgery to recognize the arrangement of motor and sensory axis cylinders. It seems probable that many of the poor results in nerve surgery are due to our failure to recognize this arrangement. As the degenerated distal sheaths act as conduits for the regenerating axis cylinders, we should have the ends of the fibers in as near a line as possible, for our results will be vitiated if motor axis cylinders pass down the degenerated fibers of sensory nerves. Until we know differently, it is well to preserve this relation, for neurotropism, as far as I know, cannot direct motor axis cylinders into the sheaths of degenerated motor fibers of the distal segment, and we have to depend on good alignment to secure this result. I believe that the good result in Dr. MacKenzie's case is due to the muscular tubulization which he performed when he sutured the muscle about the nerve fibers employed in the neuroplastic operation. Muscle has been used for tubulization, but it has its disadvantages. In the first place, muscle is subject to contraction and relaxation when in action, interfering with the caliber of the tube. A tube can be formed from fascia which will conduct nerve fibers and will not contract. The supply is practically unlimited and the fascia can be removed without interfering with function of the part from which taken — decided advantages over any other kind of autoplastic material.

BOTULISM, AN EXPERIMENTAL STUDY

A PRELIMINARY REPORT *

ERNEST C. DICKSON, M.B.

SAN FRANCISCO

An experimental study of botulism was suggested by the fact that in the investigation of an epidemic which occurred at Stanford University in the autumn of 1913, Wilbur and Ophüls[1] found that it differed from the previously reported epidemics in two important respects, namely, that the poisoning was apparently caused by the ingestion of a salad which had been prepared from home-canned beans, and that on postmortem examination of the only fatal case it was found that there was a widespread thrombosis in the blood vessels at the base of the brain and in some of the small blood vessels in the substance of the brain. Since in previous reports on botulism it has been emphasized that the condition is produced only by the ingestion of spoiled meats, and that the characteristic lesions occur only in the Nissl granules and nuclei of the nerve cells, it was deemed important to determine whether it is essential that animal protein be present in order that the *Bacillus botulinus* may produce its toxin, and whether the lesions are in fact confined to the finer elements of the nerve cells.

The facts that botulism is due to the action of a specific toxin, and that the toxin is produced by the growth of a strictly anaerobic, spore-bearing bacillus

* Read before the Section on Practice of Medicine at the Sixty-Sixth Annual Session of the American Medical Association, San Francisco, June, 1915.

* From the Division of Medicine of Leland Stanford, Jr., University School of Medicine.

1. Wilbur, Ray Lyman, and Ophüls, William: Botulism, A Report of Food Poisoning Apparently Due to Eating of Canned String Beans, with Report of a Fatal Case, Arch. Int. Med., October, 1914, p. 589.

in a pabulum which contains animal protein, were established by van Ermengem[2] during the investigation of an epidemic which occurred in Ellezelles in 1895. Van Ermengem found that the poisoning had been produced by the ingestion of spoiled ham, and he was successful in reproducing the condition in animals by feeding the ham and by injecting small quantities of the macerated ham. He also found that in the ham and in the spleen of one of the victims there was a large, gram-positive bacillus which proved to be anaerobic and spore bearing. In his further experiments he found that the bacillus itself was not pathogenic to animals which were susceptible to botulism, but that if the bacillus were grown in a medium containing meat a toxin was formed which produced the symptoms. The experiments of van Ermengen and others showed that the toxin was produced only under strictly anaerobic conditions, that it was rarely found unless the medium was alkaline in reaction, and that it was rapidly destroyed in the presence of light or air or by heating to 80 C. (176 F.). They noted that the presence of the organism was indicated by a peculiar rancid odor which strongly resembles that of butyric acid.

Botulism has long been recognized as a distinct type of meat poisoning, and many epidemics have been recorded in literature, especially in Germany. It has been most frequently observed after the ingestion of spoiled sausages and so obtained its name. With the exception of Wilbur and Ophüls' series, I have been able to find but one report of an epidemic in which the condition was recognized as botulism and which was proved to be due to the ingestion of spoiled vegetables. An epidemic occurred in Darmstadt in 1904 in which twenty-one persons became ill and eleven died after eating bean salad. Landmann[3] investigated the epidemic and proved that the beans were responsible for the poisoning. He successfully inoculated white mice with salt solution in which the beans had been macerated and he recovered the *B. botulinus* from the beans, but he concluded that the beans must have been cooked with pieces of meat because "it is not possible to cultivate botulinus on other than meat-containing medium." There have been, however, at least two epidemics in California which are of interest in this respect. In 1910, Peck[4] reported a series of eleven fatal cases of "ptomain poisoning" in which death followed the eating of "sour" home-canned pears, and in which the symptoms which he described are very similar to those observed in botulism; and quite recently there was an epidemic in Fallbrook in Southern California in which a diagnosis of botulism was made, and in which the most probable cause of the poisoning was spoiled home-canned apricots.

The symptomatology of botulism has been summarized by van Ermengem as a neuroparalytic symptom-complex with disturbances of secretion, and symmetrical partial or complete motor paralyses which apparently have their seat in lesions of the central nervous system. The first symptoms do not occur earlier than from twelve to twenty-four hours after ingestion of the infected food, although they may appear much later. In contrast to the usual types of food poisoning there is apt to be little evidence of acute gastro-intestinal disturbance, and obstinate constipation is more frequent than is diarrhea. There is usually a decrease, but there may be an increase in the secretion of saliva and of mucus in the mouth and in the throat, and when mucus is present it is extremely viscid. There is early disturbance of the external and internal muscles of the eyes which manifests itself by blepharoptosis, mydriasis, disturbances of accommodation, diplopia and strabismus. General muscular weakness is common. There may be dysphasia or aphonia and there is usually great difficulty in swallowing. The absence of sensory disturbances is characteristic.

The symptoms gradually increase in severity, and when death occurs it is usually from respiratory or cardiac failure, as in bulbar paralysis. When recovery takes place there is a long and tedious convalescence with a slow return of muscular strength. The condition so closely resembles that seen in gelsemium or hyoscyamin poisoning, poliomyelitis, cerebral syphilis and bulbar paralysis, that isolated cases may readily escape recognition, but when a series of cases is seen, and especially if all have partaken of a common article of food, there is usually little difficulty in establishing a diagnosis.

Although the symptoms are essentially those indicative of involvement of the central nervous system, comparatively few brains of human victims have been carefully studied. Almost all of the observations on the type of the pathologic lesions have been made on the brains and cords of animals in which the poisoning has been experimentally produced. Van Ermengen[2] made a careful study of the tissues from the animals of his original series and he described, as the most important lesion, a type of degeneration in the Nissl granules of the ganglion cells. The lesions were most marked in the cord and were almost entirely restricted to the cells in the motor portions of the cord. They were less numerous in the medulla, pons and peduncles, and were almost entirely absent in the forebrain. He also described a hyperemia of the blood vessels in all the organs, and he believed it to be a primary hyperemia because of the presence of degenerative processes in the endothelial cells, and of numerous "microscopically diffuse" hemorrhages in the intestine, stomach, liver, kidneys, lungs, muscles and central nervous system, especially about the cord and medulla. He noted leukocytic infiltration in many of the organs, and early parenchymatous degeneration in some. Marienesco[5] also studied the brains and cords of the animals of van Ermengem's series and his findings agreed with those of the latter. The lesions of the Nissl granules seem to have attracted the most attention, and their occurrence was confirmed by Kempner and Pollack,[6] Römer and Stein[7] and Ossipoff,[8] although the latter author made the additional observation that within the hyperemic blood vessels, as well as on the outside, there were many white blood corpuscles, and that within the blood vessels these leukocytes were often "bunched in masses."

In the examination of the tissues of the patient who died in the Stanford University epidemic, Ophüls[1] found a well-marked thrombosis of the vessels of

2. Van Ermengem: Ztschr. f. Hyg. u. Infectionskrankh., 1897, xxvi, 1; Arch. de pharmacod., 1897, iii, 213, 499; Handb. d. path. Microorg., Kolle und Wassermann, 1912, iv, 909.
3. Landmann: Hyg. Rundschau, 1904, xiv, 449.
4. Peck: South. California Pract., 1910, xxv, 121.
5. Marienesco: Presse méd., 1897, v, 43.
6. Kempner and Pollack: Deutsch. med. Wchnschr., 1897, xxiii, 505.
7. Römer and Stein: Arch. f. Ophth., (Graefe's), 1904, lviii, 291.
8. Ossipoff: Ann. de l'Inst. Pasteur, 1900, xiv, 769.

the meninges and of the brain, a type of lesion which had not previously been described. Thrombi were present in the right vertebral artery, in the basilar artery and several of its branches, in the veins around the medulla and pons, and in the vessels of the tela choroidea. There were also thrombi in many of the blood vessels in the substance of the stem, some of them being in close proximity to the important nuclei. The thrombi contained much fibrin and many leukocytes but there were very few conglutinated blood platelets. In the cortex of the cerebrum there was marked hyperemia but no thrombi. The Nissl granules appeared to be normal. There was marked hyperemia of the abdominal viscera. One small thrombus was found in a vein of the intestinal submucosa and a few in the cortex of the ovaries, but there was no evidence of a general tendency to thrombosis.

The normal habitat of *B. botulinus* is not known, although Kempner and Pollack[8] succeeded in cultivating the organism from pig's feces. It is of interest that in the reports of two of the California epidemics it was noted that the people lived in unhygienic surroundings, and that pigs were kept near the house, but it is impossible to say whether this had anything to do with the contamination of the foodstuffs.

Fig. 1.—Thrombosis in vein in deep sulcus of cerebrum of Cat 35. Note the large number of leukocytes which are enmeshed in the fibrin. (Toxin from canned beans.)

As I have already stated, the object of our experiments was twofold: first to determine whether it is possible for the toxin of botulism to form in a vegetable medium, and second, to see whether the lesions that result from the intoxication are confined to the nerve cells of the central nervous system. The first series of experiments were carried out as follows: About 1 c.c. of a suspension of *B. botulinus* in normal saline was injected through a nail-hole in the tops of cans of string beans which were then resealed with solder. The beans were obtained from a grocery store and were high-grade, one-quart cans, and the strain of *B. botulinus* was obtained from the New York Museum of Natural History. The cans were allowed to incubate at room temperature for periods of from three to twelve months, after which they were opened, the reaction of the contents was tested in nearly all cases, aerobic and anaerobic cultures on various mediums were made, and portions of the fluid from the cans were injected into guinea-pigs, rabbits and cats.

In order to supplement the first series of experiments another series was undertaken in which infusions of canned string beans, canned peas, pork and beef were inoculated with the same strain of *B. botulinus* as was used in the first experiments, and with another strain which was obtained from Prof. Hans Zinsser of Columbia University. In the second series the mediums were made alkaline to phenolphthalein, and about 1 per cent. of glucose was added as was recommended by van Ermengem. Anaerobic conditions were produced by covering the fluid mediums with a thick layer of liquid petrolatum. The cultures were incubated at from 22 to 28 C. for from three weeks to two or three months. The meat infusions were used to determine whether the toxin which was produced in a meat medium would produce the same type of lesions as that which was produced in a vegetable medium. The inoculations were made in the same species of animals as were used in the first series.

In Series 1, twelve cans of beans were inoculated in the manner described, but four of them were later discarded because four of the control animals died shortly after they had been inoculated with fluid from the cans. It may be stated, in passing, that the cause of death in the four control animals was not ascertained. The reaction of the contents of the cans after incubation ranged between 1.7 and 3.2 per cent. acid to phenolphthalein, the majority varying from 2 to 2.5 per cent.[9] From six of the cans *B. botulinus* was recovered in pure culture. Sixteen guinea-pigs, 16 rabbits and 13 cats were injected with the fluid from the cans, and of these, 4 guinea-pigs, 7 rabbits and 5 cats died as a result of the injections. A number of the animals showed some symptoms for a few days after injection but eventually recovered. Of the 16 animals which died, 13 (3 guinea-pigs, 6 rabbits and 4 cats) showed the characteristic lesions which will be described below.

The proportion of the animals of Series 2 which succumbed to the injections cannot be given at present as the experiments are not yet completed and there are still a number of animals under observation However, there are 22 cases in which death occurred after inoculation and which show the same type of lesions as was found in the animals of Series 1. Of these, 1 guinea-pig, 1 rabbit and 2 cats were injected with infusion of canned string beans, 2 guinea-pigs and 1 cat were injected with infusion of canned peas, 3 guinea-pigs, 3 rabbits and 4 cats were injected with beef infusion and 2 guinea-pigs and 3 rabbits were injected with pork infusion.

Van Ermengem has described the symptoms of botulism in animals as follows: In rabbits the appearance is that of a more or less marked local or general paralysis. The animals remain motionless with the front legs stretched out, the hind legs drawn close to the body and the head turned to one side. Respiration is shallow and stertorous. The pupils are dilated, there may be exophthalmos, and the nictitating membrane is flaccid. There may be retention of the urine and feces. At times there may be clonic convulsions, and the animal frequently utters a loud cry during the death struggle. In guinea-pigs the appearance is very similar. The first indication of poisoning may be a relaxation of the abdominal muscles which can be easily made out by palpation. The

9. The reaction is given in terms of the standard recommended by the American Public Health Association for the standardization of the reaction of culture mediums.

animals lie motionless with all the legs extended. Frequently in the more chronic cases there is a persistent prolapse of the penis. In cats the symptoms are so characteristic as to be pathognomonic. There is early mydriasis and often paralysis of the lids. There is frequently aphonia, a croupy cough due to the presence of thick mucus in the larynx, dribbling of mucus from the mouth and prolapse of the tongue. There may be retention of the urine and feces and complete anorexia. In the acute cases there may be complete paralysis of the voluntary muscles, but in the chronic cases the paralysis may be local and may persist for weeks. In some cases in which the progress of the condition is prolonged there may be only a progressive cachexia which may persist for weeks.

In the majority of our cases the more acute manifestations of the poisoning were absent and the animals survived for from three to six or seven weeks after the administration of the poison, but a few died within ten days after inoculation, and in these the symptoms corresponded closely to those described by van Ermengem. In the cats especially the symptoms were very noticeable and there was no difficulty in recognizing the symptom-complex that has been described.

At necropsy in the fatal cases the characteristic hyperemia of the abdominal viscera was well marked in nearly all cases, and in a moderate number there was a definite enlargement of the spleen. In a few cases the *B. botulinus* was recovered from the spleen, but as a bacteriologic examination was not made in all cases it is impossible to say in what proportion they may be found. The meninges of the brain were usually congested and occasionally macroscopic hemorrhages were seen. In fact the gross appearance of all the organs was identical with that which has been described by van Ermengem and others.

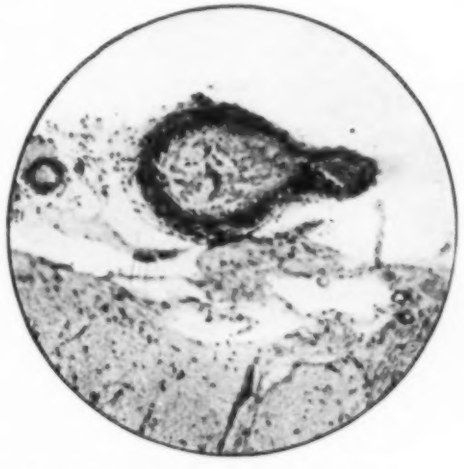

Fig. 2.—Thrombosis in posterior cerebral artery. Guinea-pig 53. (Beef infusion.)

In the present report no attention will be paid to the microscopic pathology of any of the organs excepting the brain and the upper portion of the cord, as the study of the other organs has not yet been completed. In the brain the lesions correspond accurately to those which were observed by Ophüls in the case which he and Wilbur reported. The vessels of the meninges and of the brain are all much congested, and it is not at all uncommon to find large and smaller hemorrhages in the meninges, especially in the folds in the sulci of the cerebrum and the cerebellum. A very frequent seat of hemorrhage is in the dorsal sulcus of the stem beneath the posterior portion of the cerebral hemispheres. At times the hemorrhages are strictly confined to the meninges, but very often they invade the peripheral portion of the brain tissue for varying distances. At times there are also small and larger hemorrhages in the tissue of the brain, and these have been seen in the stem, in the cerebrum and in the cerebellum.

The most striking feature in these cases, as also in Wilbur and Ophüls' case, has been the presence of thrombus in the blood vessels of the meninges, and occasionally of the brain itself. In the case in which but little thrombus is found it is more frequently situated in the veins of the folds of the meninges within the sulci of the cerebellum and the cerebrum or between the cerebrum and the stem. In other cases in which there is more thrombosis, practically all of the large and smaller veins of the meninges as well as many of those in the tela choroidea may be involved. In a fair percentage of cases the arteries also contain thrombi, and in a few cases thrombi are seen in the small vessels in the interior of the brain.

The appearance of the thrombus varies considerably. At times it consists of dense masses of fibrin in which neither leukocytes nor conglutinated blood platelets are seen, but more frequently there are many leukocytes enmeshed in the fibrin so that it appears as a closely packed mass of cells. At times there are masses of conglutinated blood platelets in the thrombus, and in a few cases there are masses of conglutinated blood platelets in which leukocytes are embedded in places where no fibrin is seen. The appearance of these masses corresponds closely to the description of the masses of leukocytes which were described by Ossipoff.

The appearance of the lesions differs to a certain extent in each of the species of animals that was used, although, on the whole, there is a remarkably close resemblance in all. In the guinea-pigs and in the rabbits there is much greater tendency to hemorrhage than in the cats, and in the cats there is much more marked infiltration with leukocytes than in the guinea-pigs and rabbits. However, the difference is not very clearly defined and in some of the animals of all the species the lesions are practically identical.

The extent of the distribution of the thrombosis has not yet been determined. Thrombi have been seen along the upper portion of the cord, along the pons and medulla, in the meninges of the cerebellum and in the meninges of the cerebrum. Complete examination of the whole of the central nervous system has not yet been made, but it seems probable that the lesions which occur are secondary to disturbances of blood supply. That certain groups of vessels are usually involved is indicated by the uniformity of the clinical symptoms, but there seems to be no doubt that lesions may be found in any part of the central nervous system, their location being dependent on the more or less accidental distribution of the thrombosis. It has not as yet been ascertained that the thrombosis is restricted to the vessels of the central nervous system. Further study of the different organs of the body is necessary before this point can be settled.

In Series 1 of these experiments in which it has been shown that the toxin of botulism may develop in peas and beans in which the *B. botulinus* has grown, the significance is very evident. Leuchs[10] recorded that Professor Gaffky had told him that he had succeeded in growing the Darmstadt strain of

10. Leuchs: Ztschr. f. Hyg., 1910, lxv, 55.

B. botulinus on a bean medium, and that the toxin had been produced, but I have been unable to find any detailed description of Gaffky's experiments, and it has not been generally understood that such experiments have been performed. The prevailing impression concerning botulism is that the toxin is produced only in the presence of animal protein and in an alkaline medium, and that there is no danger of this particular type of food-poisoning from the ingestion of spoiled vegetables and fruits. The danger of improperly prepared canned meats is so well known that few people attempt to prepare them at home, but the canning of fruits and vegetables is thought to be perfectly safe, and large amounts of fruit and vegetables are canned at home each year. That the methods of sterilization in home canning are inadequate is shown by the fact that it is not at all uncommon for the housewife to find that some of the cans of fruit and vegetables have spoiled. The U. S. Department of Agriculture[11] has issued bulletins in which is emphasized the importance of fractional sterilization of all canned goods which are preserved at home. In canning factories where the danger of contamination with spore-bearing bacteria is understood and where sterilization is done with steam under pressure, there is little danger of contamination, but when the material in the cans is subjected to a single sterilization with live steam, there is very grave danger if the food or the cans happen to contain spores.

That canned goods form an ideal location for the growth of the *B. botulinus* and for the development of the toxin, there can be no doubt. The organism is an obligative anaerobe which forms its toxin best in the dark and at a temperature of from 22 to 28 C. (71.6 to 82.4 F.). The spores resist a temperature of 85 C. (185 F.) for nearly half an hour, and it is extremely doubtful whether in the ordinary method of steaming the cans for an hour, or even more, in a loosely covered wash-boiler, the temperature in the centers of the cans is maintained at a point sufficiently high to kill the spores.

The important facts that have been established in the first series of experiments are two in number; first, that the toxin of botulism may develop in a vegetable medium to which no meat has been added, and second, that the acidity of the ordinary canned vegetables does not prevent its formation. The investigation has thus far been restricted to canned string beans and canned peas; but if we can accept the evidence of the two series of cases in Southern California, there seems to be little doubt that certain fruits as well as certain vegetables may furnish suitable pabulum for the development of the toxin.

The demonstration of the thrombosis in the blood vessels and of the hemorrhages in the meninges and in the brain is of more purely academic interest. Their presence indicates that there must be some specific action on the circulatory system which causes increased permeability of the vessel walls and which promotes thrombosis. Whether there is a primary damage of the endothelial cells, as was suggested by van Ermengem, remains to be proved, but whatever may be the explanation for the changes which occur in the blood vessels, there is little doubt that the changes which are found in the structure of the nerve cells are secondary to diminution of the blood supply. One can much more readily understand the variations in the clinical course of patients affected with botulism on the basis of local disturbances of blood supply than on that of specific damage to certain groups of nerve cells. The fact that, as a rule, the majority of patients recover may depend on the fact that a fatal termination is dependent on the accidental location of the thrombus in vessels which provide the blood supply to those portions of the brain which contain the vital centers. It is significant that in the experimental cases in which the subject succumbed most quickly there was a much more widespread thrombosis than in others in which death followed more slowly. It may well be that in the more virulent epidemics a larger number of the vessels are affected and that there is therefore greater chance of the vital centers becoming involved.

11. Bull. U. S. Dept. Agric., Farmer's, Nos. 262 and 359.

CONCLUSIONS

1. The presence of animal protein is not essential for the development of the toxin of botulism.
2. The toxin may be produced in a medium made from string beans or from peas.
3. An acid reaction of as much as 3.2 per cent. to phenolphthalein does not prevent the formation of the toxin.
4. The toxin produces some disturbance of the circulatory system which leads to hyperemia and hemorrhages in the meninges and in the central nervous system, and to thrombosis in the arteries and veins of the meninges and of the central nervous system.
5. The lesions in the nerve cells are not due to a specific action of the toxin on the cell protoplasm, but they are secondary to disturbances of blood supply.

THE EARLY DIAGNOSIS OF MASTOIDITIS*

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There is no experience in the life of the otologist that is more pathetic than to be called in consultation a few weeks after the onset of an acute purulent inflammation of the middle ear, to find a patient with a history of recurrent chilly sensations, temperature from 100 to 105 degrees, anxious expression, clammy skin, symptoms of a lateral sinus involvement, or to find the patient with a rapid pulse, high temperature, headache, contracted pupils, anxious look, often delirious, and symptoms sometimes of meningitis. In either condition the prognosis is grave, and in the latter more so than in the former. I want to go a little further than the subject implies, and discuss indications for early operation and say a word about who should operate.

It may be stated that the earlier a case of mastoiditis is detected and given operative treatment, the earlier and more complete the recovery, and more positive the preservation of normal hearing during the life of the individual. It is remarkable the number of cases of so-called catarrhal deafness and middle ear sclerosis that apply for treatment, showing scar tissue in the drum membrane, evidence of a discharging ear at some time in life, many times the early occurrence of the disease having been forgotten. There is a class of patients with partial or complete absence of drum

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Probably in every case of middle ear abscess with spontaneous rupture of the tympanic membrane, and likewise most cases when paracentesis is delayed, more or less involvement of the mastoid has occurred,

Fig. 4.—Mastoid cells obliterated by a process of eburnization. No white spots or cells visible as in Figure 3, the opposite mastoid.

and in the beginning is a serous or seropurulent exudate and sometimes pus. The cases that recover most rapidly after operation are those in which operation is performed before bacteria have invaded the serous or seropurulent exudate. If an early operation is

Fig. 5.—Normal mastoid. Septa separating cells distinct.

worth anything, how are we to know when a case will recover without operation, and when operation is indicated?

Many cases of mastoiditis recover without operation, and recovery is hastened by early paracentesis. It may be said that a mastoid with an infection, going to spontaneous recovery, is more liable at some future time to become the focus of a new infection, than a mastoid that has never been involved. This remark is based on the observation that a number of cases in which operation is performed for acute mastoiditis show an unusual amount of cell obliteration, which is not normal or due to the sclerotic changes of age, and must have been due to old inflammation. The amount of bacteria found in the exudation from the middle ear after a paracentesis will aid in forecasting in a measure the final outcome. Absence of bacteria, or very few, in the very beginning of the disease is favorable to early recovery. A mixed infection indicates a probable extension of the disease to the antrum and mastoid cells.

The less tension of the pus in the middle ear and antrum shown by the absence of pulsation in the secretion as it flows from the opening in the drum membrane, the less liability of involvement of the mastoid cells. The more pronounced the tension as shown by pulsating discharge from the middle ear, the more possible the mastoid involvement, and in consequence the more certain are the indications for early operation. Temperature in simple middle ear infection after paracentesis or spontaneous rupture of the drum should disappear very quickly. If it persists, the mastoid is involved.

Fig. 6.—Round white spot is the external auditory canal. Posterior bony wall destroyed as described in text. Darkened area to right of canal is mastoid cavity filled with cholesteatomas.

Tenderness in some regions of the mastoid is a valuable sign, but may be absent even when the mastoid cells are full of pus. Pain in some region of the head on the affected side is usually present.

The two most valuable signs of mastoiditis are pulsating discharge from the middle ear, and temperature. With these symptoms a case may go to spontaneous recovery in from ten days to two months. Nevertheless, these two symptoms alone should suggest early operation.

The diagnosis of a chronic mastoiditis is often more difficult than the diagnosis of an acute mastoiditis.

membrane and ossicles, the result of suppuration and healed mastoid, and progressive deafness. Many such patients come for relief at the productive years of life and are dependent from an economic sense on good hearing. There is an unusual indifference both among physicians and the laity in regard to the danger of a discharging ear. Advisedly speaking, those with a chronic discharging ear submit to an operation only when pain or one of the severe complex symptoms of a chronic mastoiditis drives them to consult an aurist.

The uniform good results in the hand of the man skilled in surgery of the mastoid are not appreciated except by a few. Otherwise, many who attempt the operation would do so only under exceptional conditions. Among the bad results that not uncommonly follow operation by those not familiar with surgery of the mastoid are deformity, slow healing often extending over a number of years, facial paralysis, and persistent discharge from the auditory canal. Such a series of bad results can be nearly completely pre-

Fig. 1.—Area of light indicates normal cells; irregular areas of dark shadows are cells filled with fibrous exudate. Compare with normal mastoids shown in Figures 3 and 5.

vented by educating the public to a knowledge of the results obtained by the skilled otologist, as compared to the general surgeon who has performed but few such operations.

The surgery of the ear, nose and throat owes its advance to skilled men and specialists in these regions, and no one not prepared for such work by a skilled preceptor should be permitted by public opinion to undertake major operations. It is my custom in lecturing to a senior class to dwell on the symptoms and diagnosis of mastoid disease, ignoring altogether any reference to the surgical technic of mastoidectomy. There is no excuse for the young graduate being imbued with the idea that the day he enters the profession he is prepared to do such operations as a gall-bladder, a thyroidectomy or a mastoidectomy.

During the past winter I have operated in three cases in which the surgeon had failed by lack of special training. One case was an attempted cure of a chronic mastoiditis with cholesteatoma by doing a simple mastoidectomy. Another was a Wilde incision for the relief of an acute purulent mastoiditis.

The foregoing observations have a bearing on the title of the paper, for I want to recall some of the

Fig. 2.—More distinct light areas than in Figure 1; exudation into cells not so profound as in Figure 1, though recovery much slower.

early symptoms of mastoiditis and the good results which attend early surgery by surgeons who are especially trained.

The question has been asked me, "When does a case of mastoiditis become an emergency operation?"

Figure 3.—Normal mastoid cells. Cells and septa white and distinct.

The time to operate in a case of acute mastoiditis is as soon as the diagnosis is established. This does not mean that all patients will submit to operation, or that a case of acute mastoiditis will not recover apparently without operation.

Those with chronic discharge in all probability have, if not some active process in the mastoid, some disease of the antrum. The destruction of bone may be all out of proportion to the clinical signs. Continued pain on the side of the head, with or without temperature, and a history of discharging ear at some time on that side, is highly suggestive of a diseased mastoid. Blood examination of either acute or chronic mastoiditis as a diagnostic aid is of some value, but cannot change the clinical or Roentgen-ray signs, and in consequence is unnecessary from a practical standpoint. In those cases in which vaccine therapy may be contemplated, its value is inestimable.

The value of the Roentgen ray in the hand of an experienced roentgenologist, as an aid in determining any involvement of the mastoid cells, is beyond dispute. This method of diagnosis for years has had the indorsement of leading otologists. In spite of their advice, very few men in our specialty are employing this method of diagnosis today. The interpretation of

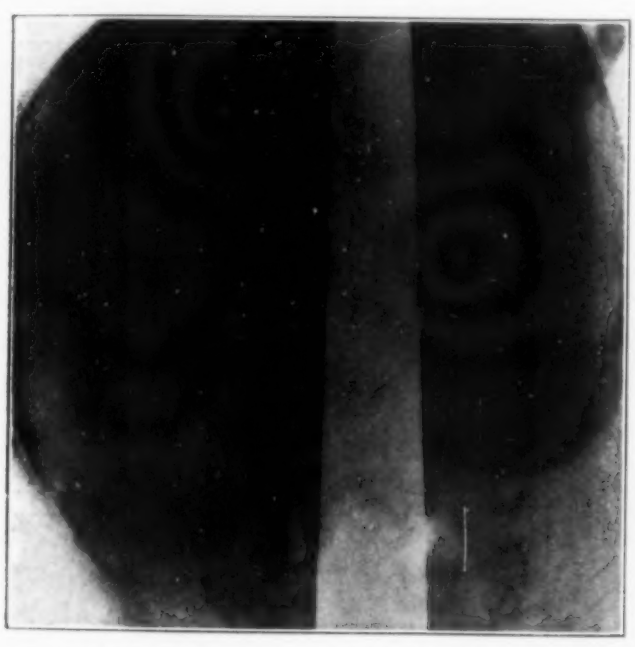

Fig. 7.—Semicircular canals and cochlea unfortunately do not show distinct in picture. Plate exhibited at meeting of section showed superior and horizontal canals and cochlea clear and distinct. Picture taken anteroposterially.

plates should be by the otologist and not by the roentgenologist. The clinical experience of the roentgenologist is in but few cases sufficient for him to recognize other than that the mastoid is abnormal. The clinician may be able to tell, in comparison with the normal mastoid, whether a mastoid is filled with a hemorrhagic exudation, pus, cholesteatoma or sclerosed bone. A subperiosteal abscess alone or accompanying a mastoiditis may sometimes be diagnosed. The position of the head on the plate will govern the value of the picture. The head should be inclined at an angle of about 25 degrees. For comparison it is necessary to take a picture of both mastoids, and unless this is done, in many cases a diseased mastoid may be passed as a normal mastoid. Many of the cells may look so distinct that cloudiness is detected only by comparison.

The Roentgen ray will show advisedly a condition often observed in a mastoid going to spontaneous recovery and, after the drum membrane has healed, a remaining exudation in the cells, with a beginning sclerosis of the cells or eburnization. This is a pathologic change that subsequently produces a deafness.

Fig. 8.—Normal mastoid, anteroposterior view.

The deafness may be so slight that the patient makes no complaint, but in after years the deafness becomes perceptible. A careful examination at time of recovery will demonstrate often a loss of both air and bone conduction.

Fig. 9.—Opposite mastoid as shown in Figure 8. Cloudiness of mastoid due to sclerosis from old mastoiditis at time of operation; dura in region of mastoid thick and hyperemic; evidence of old localized meningitis.

Figures 1 and 2 show the right and left mastoid cells of a patient having recovered from an acute double middle ear abscess, the symptoms of double mas-